Underreporting of Fatigue in Gynecologic Oncology Patients

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ABSTRACT

Background and Significance: Cancer-related fatigue (CRF) is a well-documented symptom among gynecologic oncology patients. However, there is little known about the etiology, and treatment options are currently suboptimal. While the lack of knowledge surrounding the intricacies of CRF impedes effective care, there is arguably a more serious barrier to delivering adequate treatment. Fatigue symptoms are highly underreported to physicians making it impossible to offer treatment to a large subsection of patients. This study will focus specifically on gynecologic oncology patients, a population with a staggering prevalence of CRF.

Research Question: The purpose of this study is to identify clinical, psychosocial, and lifestyle characteristics that may be associated with the underreporting of fatigue specifically in gynecologic oncology patients.

Methods: The design of this study is a cross-sectional survey. 89 subjects were recruited from three outpatient sites. Inclusion criteria included: (a) women age ≥18 years old with a known ovarian, uterine, cervical, vaginal, vulvar, or primary peritoneal cancer; (b) Currently attending physician's office hours and/or undergoing chemotherapy at one of the above listed centers. This study will focus specifically on the reporting of CRF in gynecologic oncology patients.

Results: Results showed that barriers to reporting fatigue were significantly correlated with the chemotherapy cycle a patient was undergoing. Additionally, the date of last treatment, a patient's weight, and the cancer stage was associated with higher levels of underreporting in this population.

Conclusion: The prevalence of cancer related fatigue is staggering; however, there is limited research as to why patients are underreporting such a significant symptom to their health care team. With the knowledge from this study, screening for fatigue can become more efficient by targeting women in specific chemotherapy cycles. Practitioners can also use this data to identify patients with high-risk characteristics that might contribute to their unwillingness to discuss fatigue symptoms.

TABLE OF CONTENTS

Introduction 1

Materials and Methods 5

Results 8

Discussion 13

Future Directions/Conclusions 14

References 15

TABLES

Table 1: Barriers to fatigue relief and management 4

Table 2: Correlations between clinical characteristics and mean FMBQ scores 10

Table 3: Summary of statistically significant variables of multiple regression analysis 11

Introduction

Fatigue is a well-known symptom among cancer patients and its effects often have a significant impact on quality of life. Curt et al. reported fatigue was ranked as the longest lasting and most disruptive symptom by cancer patients[1]. The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as a persistent subjective sense of physical, emotional, and/or cognitive tiredness related to cancer or cancer treatment that is not proportional to activity level and significantly interferes with usual functioning[2]. Multiple organizations have variations of a similar definition, but regardless of how you define it, there is a negative impact on a patient's overall well being. In a study of gynecologic oncology patients undergoing treatment, CRF affected nearly 96% of the women surveyed[6]. Other studies have reported prevalence ranging from 50%-90% spanning multiple types of cancer[4]. The variations among studies are not surprising due to a lack of commonly accepted diagnostic criteria and assessment tools. Despite these staggering numbers, there is limited insight into the multifaceted etiology of CRF and treatment is currently sub-optimal. The burden of CRF is significant and only continues to grow as life expectancy among cancer patients increases[9].

The etiology of CRF is complex, involving a vast array of potentially contributing factors[12]. It is important to note CRF is a unique diagnosis and may not be related to well recognized physiologic factors, such as anemia. Holzner et al. examined the prevalence of fatigue in ovarian cancer survivors with hemoglobin levels over 10 g/dL, and still ~30% of patients reported suffering from fatigue[6]. Dating back to the 1990's, researchers have studied the theory that inflammation may play a role in a multitude of cancer related symptoms including fatigue, pain, poor appetite, sleep disturbances, and others. These symptoms often occur together and may have similar onsets making it plausible that systemic inflammatory effects contribute to the myriad of symptoms cancer patients' experience. Preclinical research has shown that signals from proinflammatory cytokines, primarily interleukin (IL)-1β and tumor necrosis factor (TNF)-α, promote neurologic changes that result in sickness behaviors, including fatigue and other previously mentioned symptoms[19]. Another prominent theory describes CRF being related to disruptions in metabolic activity, either by the cancer itself or as a sequela of

treatments. Tumors, infection, and surgery are all associated with hypermetabolic states leading to an increase in energy demand and a decrease in available substrates needed to maintain normal metabolism[19]. In conjunction with these theories, it is known that behavioral and psychological changes such as inactivity, stress, depression, and nutritional deficiencies contribute to the development of CRF[9]. However, based on current literature, there is no single hypothesis that can conclusively explain the mechanism of CRF. At this time, CRF is best explained as an elaborate, synergistic relationship between physiologic, psychosocial, and behavioral factors.

Due to the difficulty of defining the pathogenesis of fatigue, treatments for patients are limited and often lack success. The specifics regarding different treatment modalities is out of the scope of this paper; however, it is important to note that most methods are somewhat controversial and have inadequate evidence based support. Based on the NCCN guidelines for CRF interventions, nonpharmacologic treatments should be considered before initiation of pharmacologic therapies, such as psychostimulants[2]. However, Jacobsen et al. conducted a meta-analysis of 30 studies evaluating the efficacy of psychological and activity-based interventions against CRF and found <50% of the trials rated “fair” or better in quality yielded significant findings favoring the studied intervention[11].

While the lack of knowledge surrounding the intricacies of CRF impedes effective care, there is arguably a more serious barrier to delivering adequate treatment. Fatigue symptoms are highly underreported to physicians making it impossible to offer treatment to a large subsection of patients. In a study of >500 patients in an outpatient setting, 52% (281 of 538) of participants who had experienced at least some level of fatigue never reported the issue to their hospital doctor[17]. Multiple studies report that between 50-74% of patients are under the impression fatigue is an untreatable symptom and is a normal part of cancer and the subsequent treatment[14,17]. Barriers to the recognition and treatment of fatigue can be subcategorized into three groupings: patient, healthcare provider, and system barriers[3]. A further description and examples within these categories can be found in **Table 1**.

This study will focus specifically on the reporting of CRF in gynecologic oncology patients. CRF has a staggering prevalence and severity in patients with gynecologic cancer. Due to advancements in screening methods and treatments, patients with gynecologic cancers are living longer yet still suffer from the debilitating effects of fatigue. In a study of 98 ovarian cancer survivors, 32 women (32.7%) were diagnosed with fatigue after being treatment free for at least 6 months[16]. The heterogeneity of most studies involving CRF makes it difficult to find correlations to a specific type of cancer and therefore customize treatment options. There are often large discrepancies in the representation of different cancers among studies. For example, in a multi-center study of 576 patients evaluating CRF, 220 patients (38%) had breast cancer while only 47 (8%) had a form of gynecologic cancer[17]. Considering gynecologic oncology encompasses a unique and diverse patient population (including young women who are not normally at risk for other types of cancer), it is essential that clear distinctions be made as to what factors deter this specific group from reporting fatigue symptoms. The purpose of this study is to identify clinical, psychosocial, and lifestyle characteristics that may be associated with the underreporting of fatigue specifically in gynecologic oncology patients.

Table 1. *Barriers to fatigue relief and management*	
Patient	Wariness regarding more pharmacologic treatment Thinking CRF is an unavoidable consequence of cancer Fear about fatigue as a symptom of disease progression Desire to be a good patient Fear of distracting their doctor Lack of awareness of non-medication interventions Lack of communication
Healthcare Provider	Failure to initiate screening protocols and/or recognize patient barriers Lack of evidence for effective treatment modalities
System	Reimbursement and regulatory constraints Lack of referrals to specialists and supportive care services

Research Methods and Materials

Procedures

The design of this study is a cross-sectional survey. 89 subjects were recruited from three outpatient sites (St. Joseph's Hospital and Medical Center, The University of Arizona Cancer Center – Phoenix, and The University of Arizona Cancer Center – Tucson). Initial chart review occurred to ascertain information regarding type of malignancy, status treatment, current hemoglobin level, BMI, and age. Eligible subjects met the following inclusion criteria: (a) women age ≥18 years old with a known ovarian, uterine, cervical, vaginal, vulvar, or primary peritoneal cancer; (b) Currently attending physician's office hours and/or undergoing chemotherapy at one of the above listed centers. Patients receiving chemotherapy agents other than Platinum or Taxane-based were excluded from this study. Informed consent was obtained prior to data collection. Surveys were administered in person at the above sites, and the research assistants were available to answer questions. All data was de-identified prior to being entered into a database for statistical analysis.

Measurement

The survey included: (a) self reported age, gender, weight/height, language spoken at home, cancer type/stage, zip code, and treatment information; (b) 1 question regarding support group participation; (c) exercise level; (d) servings of fruits/vegetables per day; (e) Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F); (f) Interpersonal Support Evaluation List – 12 (ISEL-12); (g) Fatigue Management Barriers Questionnaire (FMBQ); (h) Functional Assessment of Cancer Therapy – General (FACT-G); (i) Female Genitourinary Pain Index (GUPI). A copy of the survey is included in *Appendix a*.

The FACIT-F is a fatigue scale with questions specific to chronic illness treatment. The questionnaire includes 13 self-reported items. A 4-point Likert scale is used for answering questions (0, Not at all; 1, A little bit; 2, Somewhat; 3, Quite a bit; 4, Very much). Results range from 0-52, with scores of >35 considered to be clinically significant fatigue. This is a well-validated tool in contrast to single-item scales used to measure fatigue[5]. The survey is thought to have good internal consistency with a Cronbach's α coefficient of 0.86 to 0.87[5].

The ISEL-12 is a measure of perceived interpersonal support. It consists of 12 questions with 3 subscales including: appraisal, belonging, and tangible support. Results range from 0-36. A lower score translates to a patient believing they have less social support available. A study conducted in 2006 to validated the ISEL-12 tool reported consistent results with its original presentation in 1985[13]. Internal consistency is good with a Cronbach's α coefficient of 0.897[13].

The FMBQ assess a patient's level of concern with regards to perceived barriers to fatigue management and treatment[14]. There are 28 self-reported items with a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). It is comprised of 10 subscales including treatment futility, fear of disease progression, concern of being a good patient, fear of distracting the doctor, lack of concern, fear of stigma, general medication concerns, preference of nonmedication intervention, fear of jeopardizing cancer treatment, and lack of communication. Higher scores correlate with higher levels of concern. The survey has been validated and shows good internal consistency (Cronbach's α coefficient of 0.88[14]).

The FACT-G is used to assess quality of life in patients undergoing cancer therapy. The survey includes 27 questions with answers using a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). The phrasing of questions is so that higher numbers are indicative of a better health state; therefore, some items must be reverse-scored. The questionnaire includes 4 subscales: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-being. Cronbach's α coefficient was shown to be 0.88, representing good internal consistency[18].

The Female GUPI is used to evaluate the severity of genitourinary pain in both men and women. The tool was developed by modifying the NIH Chronic Prostatitis Symptom Index[7]. The survey includes 15 questions subcategorized into 3 groups: 10 pain items, 2 urinary symptom items, and 3 quality of life items. Scores range from 0-45 with higher scores correlating with more severe symptoms. Pain, urinary, and quality of life subscales had Cronbach's α coefficients of 0.88, 0.60, and 0.78, respectively[7]. The internal consistency is good except for the urinary subscale in women.

Data Analysis

Descriptive and inferential statistics were used in data analysis. The Kruskal-Wallis equality-of-populations rank test was used to determine whether the mean scores were statistically significantly different between categories. This test was used due to the small sample size, which would not be conducive to a normal distribution. Additionally, linear regression was used to ascertain which of the demographics and clinical characteristics were highly predictive of the scales in the data set.

Results

Patient Characteristics

This study included 89 women with an age range of 31-90 years old. The largest age group represent was women ages 51-60 making up 35.96% of the sample (*n*=32). The mean BMI for participants was 28.95 (SD, 9.46). With regards to stage number, 24.72% of patients were early stage (I-II) while 58.43% were advanced stage/metastatic (III-IV). When asked about participation in a cancer-related support group, only 15.73% of women (*n*=14) had done so. The majority of women in this study (46.97%, *n*=41) reported at least some form of daily exercise.

Patient Reported Barriers to Communicating Fatigue

The mean score for the FMBQ survey was 62.11 (SD, 20.20). Patient responses to several items are worth noting. First, 64.05% of those surveyed agreed or strongly agreed that they preferred to treat their fatigue without medications. Additionally, 60.68% of participants agreed or strongly agreed that they generally try to limit the number of medications they take. 66.3% of the women in this study disagreed or strongly disagreed that nothing could be done about their fatigue. With regards to the statement: "My doctor does not ask my about fatigue", 75.28% of participants disagreed or strongly disagreed. Based on clinical characteristics, the highest FMBQ score was 89 (SD, 2.83) for those patients undergoing their first of three chemotherapy cycles. Mean FMBQ scores arranged by patient characteristics can be found in **Table 2**.

Factors Associated with the Underreporting of Fatigue Symptoms

Kruskal-Wallis equality of population rank test was used to determine whether the difference in the mean FMBQ scores among categories was statistically significant. **Table 2** lists the mean FMBQ scores by each category and reports statistical significance based on p-values. Differences in mean FMBQ scores based on a patient's chemotherapy cycle (first, middle, or last) were found to be statistically significant. (*p*= 0.0426). For first, middle, and last cycle, respectively, mean scores were 89 (SD, 2.83), 62.37 (SD, 14.63), 76.5 (SD, 7.78).
No other category showed statistical significant between the mean FMBQ scores.

Linear regression analysis was performed find associations between total FMBQ score and patient characteristics. Detailed results from the linear regression analysis can be found in **Table 3**. The stage number and stage type of the patient's cancer (p=0.029 and p=0.001, respectively) was significantly associated with total FMBQ score. Additionally, patient weight was significantly correlated with the total FMBQ score (p=0.023). Correlation between the date of last treatment and FMBQ score trended towards significance (p=0.078).

Table 2. *Correlation between clinical characteristics and mean FMBQ scores (n=89)*

	Mean FMBQ Score (SD)	p – value*
Clinical Characteristics		
Treatment		*p = 0.3081*
Chemo	66.13 (15.63)	
Chemo + Radiation	48.25 (25.98)	
None	61.58 (22.10)	
Chemotherapy Cycle		***p = 0.0426***
First	89.00 (2.83)	
Middle	62.37 (14.63)	
Last	76.50 (7.78)	
Last Treatment		*p = 0.3183*
<1 month	58.20 (38.18)	
2-6 months	68.57 (10.11)	
6-12 months	67.50 (9.93)	
13-24 months	72.67 (5.03)	
>2 years	50.65 (27.5)	
Surgery		*p = 0.4390*
Yes	63.22 (19.23)	
No	53.89 (28.64)	
Disease Status		*p = 0.5495*
1st Chemotherapy	67.75 (12.13)	
Remission	59.20 (22.72)	
Recurrent	65.48 (16.22)	
Stage Number		*p = 0.1528*
I	62.15 (18.71)	
II	51.29 (11.69)	
III	62.58 (19.12)	
IV	61.88 (22.90)	
Stage Type		*p = 0.5196*
Early	63.40 (28.19)	
Advanced	75.57 (8.20)	
Metastatic	72.17 (10.05)	
Unknown	61.81 (29.04)	
Support Group		*p = 0.7979*
Yes	62.50 (15.22)	
No	62.12 (21.50)	
Exercise		*p = 0.8316*
Daily	63.00 (17.19)	
Weekly	60.37 (23.08)	
Never	62.00 (23.03)	
Diet		*p = 0.7078*
<1 serving*	69.75 (8.50)	
1-2 servings	61.55 (21.68)	
3-5 servings	60.79 (19.06)	
>5 servings	75.00 (23.26)	

*Kruskal-Wallis equality-of-population rank test used
*Servings are of fruits/vegetables per day
Abbreviations: FMBQ, Fatigue Management Barriers Questionnaire; SD, standard deviation

Table 3. *Summary of statistically significant variables of multiple regression analysis*

Characteristic	B	SE (B)	t	p > |t|	[95% CI]
Last Treatment	-4.430	2.276	-1.95	0.078	[-9.440, 0.581]
Weight	0.189	0.0712	2.64	0.023	[0.032, 0.347]
Stage Number	10.850	4.336	2.50	0.029	[1.307, 20.393]
Stage Type	-26.050	5.549	-4.69	0.001	[-38.264, -13.835]

Note. $R^2 = 0.7024$ (*p = 0.0062*)
Abbreviations: B, regression coefficient; SE (B), standard error; t, t statistic; p, p-value; CI, confidence interval

Discussion

The intent of this survey was to find relationships between patient characteristics and FMBQ scores to further understand why patients with gynecologic cancer may underreport their fatigue symptoms. Several of the findings discussed in this paper have the potential to impact future clinical practice. Differences in mean FMBQ scores based on a patient's chemotherapy cycle (first, middle, or last) were found to be statistically significant. (p= 0.0426). Higher scores were reported during the first chemotherapy cycle (mean = 89, SD = 2.83), which translates to patients being aware of the most barriers to fatigue management during this time frame. It has been shown that screening mechanisms help eliminate patient perceived barriers to fatigue control, and this information could potentially guide clinicians on when it would be most advantageous to screen patients for fatigue[14].

Additionally, both weight and stage number/type were significantly correlated with increasing FMBQ scores. In previous studies, religious affiliation, type of cancer, and treatment setting were the factors significantly associated with concerns about reporting fatigue[15]. This new data suggests there are multiple other confounding factors that affect the underreporting of fatigue. With regards to weight, the data may indicate that patients are attributing their fatigue to their weight rather than a cancer related cause. This may deter patients from discussing their concerns with a physician. Additionally, it was predicted that FMBQ scores would increase by ten points for each progression into a more advanced stage. This result reiterates the fact that healthcare providers need to be educating patient on potential options for fatigue management, even in the latter stages of disease. Some limitations to this study include a small sample size and the inclusion of patients with minimal fatigue symptoms.

Future Directions

In the future, a longitudinal study of gynecological oncology patients would be beneficial to see how fatigue levels differ throughout the course of the disease.

Conclusions

There are few studies that have investigated specific clinical correlates that may affect what makes patients willing to report fatigue to their providers. Furthermore, the heterogeneity of most of those studies makes it difficult to find correlations to a specific type of cancer and therefore customize treatment options. This study is unique in that it focused on a specific cancer population with known high levels of fatigue. Results showed that barriers to reporting fatigue were significantly correlated with the chemotherapy cycle a patient was undergoing. Additionally, the date of last treatment, a patient's weight, and the cancer stage was associated with higher levels of underreporting in this population. With this knowledge, screening for fatigue can become more efficient by targeting women in specific chemotherapy cycles. Practitioners can also use this data to identify patients with high-risk characteristics that might contribute to their unwillingness to discuss fatigue symptoms.

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