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Chemotherapy-induced Fatigue among Jordanian Cancer Patients: What are the Contributing Factors?

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Abstract

Background: The purposes of this study were to examine the impact of chemotherapy treatment on Jordanian cancer patients' fatigue and to correlate their fatigue with selected sociodemographic variables at the beginning of treatment and after four weeks of treatment.

Methods: This was a single group quasi-experimental correlational design study that enrolled 43 patients diagnosed with cancer who required chemotherapy treatment. Fatigue was measured according to the Piper Fatigue Scale (PFS) before starting chemotherapy treatment and after four weeks of receiving the first dose of chemotherapy. Data were collected over a period of four weeks and analyzed with descriptive statistics, the paired-sample t-test, and Pearson product-moment correlation.

Results: The study included 17 (39.5%) males and 26 (60.5%) females with a mean age of 45.98 years. Most (n=17) were diagnosed with breast cancer. Obesity was present in about 64.4% of patients. The majority (46%) received an anthracycline-based regimen. There were statistically significant differences between respondents' total mean scores of fatigue pre-treatment and four weeks following chemotherapy treatment (t= -2.31, df=42, $P<0.05$). In addition, significant differences were found in the scores for behavioral, affective, sensory, and cognitive dimensions subscales (t= -2.24, -2.19, -2.4, -2.4, df=42, $P<0.05$) between pre-treatment and four weeks after receiving the first dose of chemotherapy treatment. We observed a significant negative relationship between fatigue scores and hemoglobin levels (r= -0.04, $P<0.01$).

Conclusion: Cancer-related fatigue is common among cancer patients who received chemotherapy and result in substantial adverse physical, behavioral, cognitive and affective consequences for patient. Given the impact of fatigue, treatment options should be routinely considered in the care of patients with cancer.

Keywords: Chemotherapy, Fatigue, Piper fatigue scale

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Introduction

Fatigue, one of the most prevalent symptoms of patients with cancer occurs across all ages, genders, cancer diagnoses, stages of disease, and treatment regimens.[1,2] Cancer-related fatigue (CRF) is different from everyday tiredness, which can be reversed by rest or sleep. It is characterized by an overall lack of energy, cognitive impairment, somnolence, mood disturbance, or muscle weakness.[3] Cancer-related fatigue is a multidimensional phenomenon which evolves over time and compromises physical energy, mental capacity and the psychological condition of the cancer patient.[4]

Studies show that 82%-96% of patients who receive chemotherapy or radiotherapy suffer from fatigue during their treatments.[5,6] In the same magnitude, those with metastatic disease suffer from fatigue.[7] Cancer-related fatigue is under-reported and under-evaluated by health care givers despite the presence of growing evidence of its impact on quality of life (QoL).[8,9]

Cancer-related fatigue can be caused or potentially predisposed by various factors. A multidimensional model which includes situational, biological, physical and psychological symptoms has been proposed or CRF. In addition to situational dimensions, the inpatient status, analgesic use and cancer stage have shown significant correlation with fatigue level.[10] For a biological dimension, hemoglobin (Hb) level has been shown to be an independent predictive factor for CRF ($P = 0.02$).[10] The impact of anemia on CRF may be different depending on onset time, patient age, and co-morbidity.[11]

Despite the high prevalence of fatigue and potential negative effect on patients' activities and emotional well-being, research in fatigue is still under-developed. There are no studies that report CRF among the Jordanian population. This study is an attempt to explore fatigue among Jordanian cancer patients who are being treated with chemotherapy in Jordan. In addition, it is anticipated that this study will have the potential to motivate staff to take fatigue into consideration while providing care for cancer patients.

Materials and Methods

Design

This one group quasi-experimental correlational design examined the impact of chemotherapy treatment on Jordanian cancer patients' fatigue, as well as the relationship between selected demographic variables and fatigue.

Sample population

A consecutive sampling procedure was used to recruit potential participants for this study. The inclusion criteria included adult patients (≥18 years) with localized or metastatic tumors (solid tumors or hematologic malignancies) and who received chemotherapy for the first time. Those treated with palliative radiotherapy were included. In addition, patients were required to have Hb levels of 12 g/dl or more at the beginning of the study with no histories of cardiac, respiratory or renal failures, no history of psychiatric or mental problems and who had the ability to give verbal consent to participate in the study.

Statistical consideration

The sample size was determined by the Cohen (1988) formula. Cohen identified three levels for the effect of the sample size when using the paired sample t-test: small (0.2), medium (0.5), and large (0.8). Based on this classification and a literature review, we chose the medium effect size for comparison between two means for this study. By testing the one-tailed hypothesis at a significance level of alpha 0.05, the sample size was determined to be 43 participants. Therefore, the convenience sample of 43 participants treated at King Hussein Cancer Center (KHCC) who met the inclusion criteria, who agreed to participate and were able to complete the study measurements were enrolled in this study. The researcher interviewed each participant twice by using the designated questionnaires, the Piper Fatigue Scale (PFS) and demographic data sheet (DDS) of the study. Patients were interviewed immediately before receiving the first cycle of chemotherapy and four weeks after receipt of the first dose of chemotherapy.

Table 1. Sociodemographic characteristics of the study population.

Characteristics	Category	Frequency	%	Mean	Standard deviation	Range
Gender	Male	17	39.5			
	Female	26	60.5			
Age (years)	<50	27	62.7	45.98	13.27	21-74
	50-59	10	23.3			
	>60	6	14			
Marital status	Single	6	14			
	Married	36	83.7			
	Widow	0	0			
	Divorced	1	2.3			
Level of education	Illiterate	0	0			
	<High school	13	30.2			
	>High school	30	69.8			
Occupation	Unemployed	20	46.6			
	Employed	23	53.4			
Monthly income (JD)	<650	23	53.4			
	>650	20	46.6			
Smoking status	Non-smoker	29	67.4			
	Ex-smoker	11	25.6			
	Smoker	3	7			
Duration time to reach the hospital	<1 hour	34	79			
	>1 hour	9	21			
Type of transportation	Own car	39	90.7			
	Public	4	9.3			
	Other	0	0			
Chemotherapy dose number	1	35	81.4			
	2	3	7			
	3	3	7			
	4	2	4.7			
Type of cancer	Breast	17	39.6			
	Bladder	1	2.3			
	Colon	5	11.6			
	Lymphoma	8	18.6			
	Multiple myeloma	1	2.3			
	NSCLC	4	9.3			
	Ovarian	1	2.3			
	Prostate	3	7			
	Stomach	1	2.3			
	Testicular	2	4.7			
Type of chemotherapy	Anthracycline-based regimen: AC, FEC, doxorubicin	20	46.5			
	Platinum based regimen: FOLFOX, DCF, CG, CbG	6	14			
	Lymphoma regimen: R-CHOP, ABVD	9	20.9			
	Other: Gemcitabine, BEP	8	18.6			
Stage of disease	One	26	60.9			
	Two	14	32.2			

Characteristics	Category	Frequency	%	Mean	Standard deviation	Range
	Three	0	0			
	Four	3	6.9			
Hb level at the beginning of treatment		12.54	1.82			
Hb level after four weeks of treatment		12.23	1.68			
BMI at the beginning of treatment	<25	15	34.5			
	25-29.9	17	39.1			
	>30	11	25.4			
BMI after four weeks of treatment	<25	16	37.3			
	25-29.9	16	37.3			
	>30	11	25.4			

AC: Doxorubicin, Cyclophosphamide. FEC: 5-Fluorouracil (5-FU), Epirubicin, Cyclophosphamide. FOLFOX: 5-FU, Leucovorin, Oxaliplatin. DCF: Docetaxel, Cisplatin, 5-FU. CG: Cisplatin, Gemcitabine. CbG: Carboplatin, Gemcitabine. R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Oncovin, Prednisolone. ABVD: Doxorubicin, Bleomycin, Vinblastin, DTIC. BEP: Bleomycin, Etoposide, Cisplatin. Hb: Hemoglobin. BMI: Body mass index. NSCLC: Non-small cell lung cancer. JD: Jordan Dinar.Bleomycin, Vinblastin, DTIC. BEP: Bleomycin, Etoposide, Cisplatin. Hb: Hemoglobin. BMI: Body mass index. NSCLC: Non-small cell lung cancer. JD: Jordan Dinar.

Instrumentation

The following instruments were used to collect data from all participants in this study.

Demographic Data Sheet (DDS)

The DDS was developed by the researcher. This form included questions related to age, marital status, gender, level of education, monthly income, occupation, religion, type of cancer, stage of disease, type of chemotherapy, chemotherapy dose number, smoking, duration time to reach the hospital, and type of transportation. Body mass index (BMI) and Hb level at the beginning of treatment and four weeks from receiving the first dose of chemotherapy treatment were also recorded.

Piper Fatigue Scale (PFS)

Fatigue was assessed using the Piper Fatigue Scale (PFS), which is a multidimensional tool designed to subjectively measure the level of fatigue. This scale has been widely used in research. It has the potential to differentiate between three levels of fatigue - mild, moderate and severe. The PFS is composed of 22 numerically scaled "0" to "10" items that measure four dimensions of subjective fatigue: behavioral/severity (6 items), affective meaning (5 items), sensory (5 items), and cognitive/mood (6 items). These 22 items are used to calculate the four sub-scale/dimensional scores and the total fatigue scores. Five additional items (numbers 1 and 24-27) are not used to calculate the subscale or total fatigue scores but are recommended to be kept on the scale. The PFS is scored as follows: the total fatigue score is the sum of the scores of all items divided by 22 to maintain the score on the same 0-10 numeric scale. The scores are categorized into four levels: 0 (none), 1-3 (mild), 4-6 (moderate) and 7-10 (severe). Test-retest reliability coefficient for the PFS in this study was 0.947. Cronbach alpha for each dimension (subscale) ranged between 0.807-0.952.

Results

Patients' characteristics

There were 43 consecutive patients prospectively enrolled in the study over a period of six months (December 2012 to May 2013). The age of participants ranged from 21-73 years (mean±SD: 45.98±13.27). The majority of participants were female (n=26), married (n= 36), had a high school diploma (n=30) and employed (n=23). The monthly income of 23 (53%) participants was less than 650 Jordan dinar (JD). The majority of patients (93%) were non-smokers and 64% were overweight or obese (BMI>25).

The majority of patients had solid tumors (80%) in the early stage (93%). Breast cancer occurred in 39% of patients, Gastrointestinal (GI) malignancy in 14%, Genitourinary (GU) cancers in 14% and lung cancer in 9%. Hematologic malignancy (predominantly lymphoma) constituted only 20% of patients. The most

Table 2. Means and standard deviations of the scores on all subscales of the Piper Fatigue Scale (PFS) prior to receiving the first dose of chemotherapy treatment (N=43).

Group	Behavioral	Affective	Sensory	Cognitive	Total PFS scores
All participants					
Mean	1.27	2.86	3.8	3.9	2.96
Standard deviation	1.10	1.57	1.63	1.97	1.45
Highest score	10	10	10	10	10

frequently used chemotherapy regimen was an anthracycline-based combination (46%; Table 1).

Baseline measurements (pre-treatment)

The total PFS scores for participants ranged from 0.75 to 6.2 (mean±SD: 2.96±1.45). Almost all participants scored low on all subscales of PFS prior to their first dose of chemotherapy. As shown in Table 2, behavioral subscale scores ranged from 0.00 to 4.83 (mean±SD: 1.27±1.1), affective subscale scores ranged from 1.00 to 6.6 (mean±SD: 2.86±1.57), sensory subscale scores ranged from 1.00 to 7.8 (mean±SD: 3.8±1.63) and cognitive subscale scores ranged from 1.00 to 8.2 (mean±SD: 3.9±1.97).

Post-treatment measurements

Total participants scores on the PFS after four weeks from receiving the first dose of chemotherapy ranged from 1.83 to 7.08 (mean±SD: 5.26±1.01). As seen in Table 3, almost all participants scored high on all subscales of the PFS after four weeks from receiving the first dose of chemotherapy. The behavioral subscale ranged from 0.17 to 6.83 (mean±SD: 3.51±1.46), affective subscale scores ranged from 2.2 to 7.8 (mean±SD: 5.05±1.27), sensory subscale scores ranged from 2.4 to 8.8 (mean±SD: 6.19±1.36), and cognitive subscale scores ranged from 1.33 to 8.5 (mean±SD: 6.31±1.33).

A paired sample t-test was used for total scores and each subscale of the PFS. The paired sample t-test revealed significant differences between respondents' total mean scores of fatigue pre- and post- chemotherapy as measured by the total PFS questionnaire (t= -2.31, df=42, P<0.05). In addition, significant differences were found between pre- and four weeks post-treatment with the first dose of chemotherapy in scores for the behavioral, affective, sensory, and cognitive dimensions subscales (t= -2.24, -2.19, -2.4, -2.4, df =42, P<0.05), respectively (Table 4).

To find the relationship between the fatigue score and sociodemographic variables, we used the Pearson product-moment correlation (PPMC) and biserial correlation (BC) coefficient.

The PPMC coefficient was used to find the correlation between fatigue scores as measured by PFS and selected sociodemographic variables on a continuous level. As seen in Table 5, the PPMC showed a significant negative relationship between fatigue scores as measured by PFS and Hb level (r= -0.04, P<0.01).

We used the BC coefficient to find the correlation between fatigue scores as measured by PFS and selected sociodemographic variables on nominal and dichotomous levels. Females had high fatigue scores (r= -0.026, P<0.01) and a positive relationship between fatigue scores measured by PFS and type of chemotherapy,

Table 3. Means and standard deviations of the scores on all subscales of the Piper Fatigue Scale (PFS) at four weeks after receiving the first dose of chemotherapy treatment (N=43).

Group	Behavioral	Affective	Sensory	Cognitive	Total PFS scores
All participants					
Mean	3.51	5.05	6.19	6.31	5.26
Standard deviation	1.46	1.27	1.36	1.33	1.01
Highest score	10	10	10	10	10

Table 4: Results of paired-sample t-test for fatigue scores as measured by the Piper Fatigue Scale (PFS).

PFS subscale	Time	N	M	SD	T	df	Sig
Behavioral	Pre-chemotherapy	43	1.27	1.1	-2.24*	42	0.000
	4 weeks after first dose	43	3.51	1.46			
Affective	Pre-chemotherapy	43	2.86	1.27	-2.19*	42	0.000
	4 weeks after first dose	43	5.05	1.57			
Sensory	Pre-chemotherapy	43	3.8	1.36	-2.4*	42	0.000
	4 weeks after first dose	43	6.19	1.63			
Cognitive	Pre-chemotherapy	43	3.9	1.33	-2.4*	42	0.000
	4 weeks after first dose	43	6.31	1.97			
Total PFS	Pre-chemotherapy	43	2.96	1.45	-2.31*	42	0.000
	4 weeks after first dose	43	5.26	1.01			

particularly for patients treated with anthracycline-based regimens (r= 0.0398, $P<0.05$; Table 6).

Discussion

The findings of this study showed that patients who received chemotherapy as a primary treatment for their cancer had statistically higher fatigue scores as measured by PFS, four weeks from the first dose compared to their scores at the beginning of their therapy. Certain groups of patients were more likely to have fatigue than others. Female patients were reported to have higher fatigue scores than males. Anemic patients reported higher fatigue scores than non-anemic patients. Patients who received anthracycline-based chemotherapy had statistically higher scores of fatigue after four weeks from the first dose compared to their scores at the beginning of treatment.

Many cancer patients feel fatigued for several months or even years after their treatment with chemotherapy.[12,13] Previous studies have found that fatigue is the most common side effect of cancer treatment, including chemotherapy,[14] and it is particularly prevalent with multimodality or dose-intense treatment protocols and in those with metastatic disease.[15] The mechanism of how chemotherapy causes fatigue is poorly understood. Previous studies show that fatigue precedes, accompanies, and follows most tumors and its treatment.[16,17] It is possible that different patho-physiological mechanisms are responsible for different dimensions of CRF. We have found that anthracycline-based regimens contribute more to CRF than other non-anthracycline combinations. In prospective chemotherapy trials fatigue is commonly described, however to the best of our knowledge there are no data available that pertain to fatigue scores among chemotherapy regimens.

Fatigue has been shown to occur in female cancer patients.[18-20] A large longitudinal study has shown that the prevalence rate of CRF is higher in females compared to male cancer patients.[20,21] The biology behind this result is poorly understood.

Anemia is common in cancer patients, both as a consequence of the cancer itself or its treatment. Our cohort of patients had a mean Hb level of 12.5 g/dl at study entry and the development of anemia correlated with higher PFS. Although early studies were unable to demonstrate a clear correlation between Hb levels and the severity of CRF, a direct relationship between anemia, fatigue, and QoL has been seen in later studies that used more refined evaluation instruments such as the Functional Assessment of Cancer Therapy-Anemia (FACT-An) subscale.[22,23] Though correction of anemia is associated with an improvement in health-related,[24] it has been shown that the use of erythropoietin stimulating agents

Table 5. Results of Pearson product-moment correlation (PPMC) coefficient between fatigue scores as measured by the Piper Fatigue Scale (PFS) and sociodemographic variables on a continuous level.

Sociodemographic variables	PFS scores
Hemoglobin (Hb) level	-0.04**
Body mass index (BMI)	0.21

**Correlation is significant at the 0.01 level.

Table 6. Results of biserial correlation (BC) coefficient between fatigue scores as measured by the Piper Fatigue Scale (PFS) and sociodemographic variables on nominal and dichotomous levels.

Sociodemographic variables	PFS scores
Age	-0.23
Monthly income	0.063
Gender	-0.026**
Marital status	-0.059
Educational level	-0.042
Job	0.059
Type of cancer	0.74
Smoking	0.34
Type of chemotherapy	0.0398*
Stages of disease	-0.043
Duration time to reach hospital	-0.26
Type of transportation	-0.272
Chemotherapy dose numbers	-0.12

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level.

during chemotherapy is associated with higher mortality.[25] This leaves the door open to try other pharmacotherapies for the treatment of anemia in cancer patients.

Of note, we observed no relationship between BMI and fatigue. This could be related to the short duration (four weeks) between pre- and post-chemotherapy treatment which was an insufficient period to detect changes in BMI. BMI changes have been shown to correlate with CRF but this finding is inconsistent.[26]

We acknowledge the limitations of this study which involve the small number of a heterogeneous group of patients. Therefore the generalizability of the study findings is limited. Validity and reliability of the PFS need to be tested in a larger prospective study.

Conclusion

Cancer patients who receive chemotherapy are at risk for considerable treatment related fatigue. Therefore, fatigue should be incorporated in the routine assessment of patients who are being treated for cancer or followed after the end of therapy. Fatigue is influenced by Hb level, gender and type of chemotherapy. Therefore, these factors should be taken into account when caring for cancer patients.

Conflict of Interest:

No conflict of interest is declared.

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