Sudden Loss of Ovarian Function Exacerbate Cancer-related Fatigue in Patients with Ovarian Carcinoma

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Abstract

Objective: We aimed to investigate whether ovarian cancer and cancer-related fatigue are associated with a sudden loss of ovarian dysfunction.

Methods: In total, we retrospectively analyzed 211 survivors of ovarian carcinoma from the First Affiliated Hospital of Soochow University between January 2015 and January 2020. Fatigue was measured with the Cancer Fatigue Scale (CFS). Single and multiple linear regression were used to determine statistical differences.

Results: Fatigue was reported in 206 of all completed questionnaires. Patients who had a menstrual period prior to treatment had a higher fatigue score. The CRF score was highest during the first two years after treatment and gradually decreased over time. Patients with sleep disorders became fatigued more easily. We identified a negative correlation between hemoglobin and CRF. There were no significant correlations between CRF, the number of chemotherapy cycles, the type of chemotherapy regimen, or the pathological subtype of ovarian cancer.

Conclusion: CRF is common in ovarian cancer patients and improve CRF are important for improving the quality of life. The fatigue experienced by patients with ovarian cancer may be related to the deprivation of sex hormones. It may be prudent to add such hormones to the treatment regimen in order to improve CRF.

Introduction

Ovarian cancer is associated with the highest mortality rate of all gynecological tumors and can lead to serious sequelae with regards to health-related quality of life (HRQoL). Patients suffering from ovarian cancer can experience cancer-related fatigue (CRF) that is caused by the disease itself. Little is known about the treatment for this condition. Cancer-related fatigue (CRF) is a common symptom and can exert severe effects on numerous aspects of a patient's life. However, CRF is largely neglected by doctors and patients and we know very little about how to treat this condition. However, developing methods to evaluate and treat CRF would be highly beneficial for the patient.

According to the recommendations of the National Comprehensive Cancer Network (NCCN), CRF is defined as a subjective feeling of physical, emotional or cognitive fatigue or exhaustion resulting from the cancer itself or cancer-related treatment that is not proportional to the amount of recent activity and interferes with the patient's ability to function normally. [1] The NCCN suggests that all patients with cancer must be investigated for CRF throughout the course of their diagnosis and treatment. [2]

Very few studies have investigated the relationship between physiological status and hormone levels in ovarian cancer patients suffering from CRF.

The primary aim of this retrospective study was to examine the prevalence of CRF in women who had undergone treatment for ovarian cancer to investigate whether there were any relationships between CRF and a range of clinical characteristics. Our findings are expected to provide a clearer understanding of the effects of fatigue in patients with ovarian cancer.

Materials And Methods

Patient Selection

We investigated patients with a diagnosis of ovarian carcinoma who were hospitalized between January 2015 and January 2020 in the Department of Gynecology at the First Affiliated Hospital of Soochow University. This research was approved by the local ethics review committee. Patients were included if they (1) had a definitive diagnosis of ovarian carcinoma, (2) had no form of mental or cognitive impairment, (3) spoke Chinese, and (4) provided informed consent. Patients were excluded if the patients had severe mental or physical diseases at the time of investigation.

Socio-demographic and Clinical Characteristics

Once patients were recruited, we collated a range of personal and medical information, including age, gender, menopause status, time since treatment, pathological subtype, type of chemotherapy, the use of hemoglobin following surgery, and the form of treatment.

Assessment of Fatigue: the Cancer Fatigue Scale

In this study, we used the cancer fatigue scale (CFS) described by Uchitomi et al. The CFS is a 15-item self-reporting instrument that was designed to measure fatigue in three domains: physical fatigue (7 items), affective fatigue (4 items), and cognitive fatigue (4 items). Each item is assessed on a 5-point Likert scale where '1' represents 'no' and '5' represents 'very much.' The possible scores range from 0 to 28 for the physical domain, 0 to 16 for the affective domain, and 0 to 16 for the cognitive domain. The specific scoring methods are as follows: physical fatigue = (items 1 + 2 + 3 + 6 + 9 + 12 + 15)-7; affective fatigue = 20 - (items 5 + 8 + 11 + 14), and cognitive fatigue = (items 4 + 7 + 10 + 13)-4, as described previously [3]. The sum of the domains (0–60) represents the total fatigue range; higher scores indicate a higher degree of fatigue. Based on previous studies, we defined clinically relevant fatigue as a global CFS score $\geq 18/19$. The Chinese version of the CFS has been reported to have good internal consistency and validity [4].

Statistical Methods

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software version 26.0(IBM Corp, Aemonk, NY). Descriptive statistics for clinical variables are reported as the mean ($\pm$ standard deviation, SD) of continuous data and as the proportion (%) of categorical variables. Linear regression analysis was used to determine potential predictors for the severity of fatigue. Simple linear regression, with dummy variable coding and one-way analysis of variance (ANOVA), was conducted to analyze specific relationships between clinical variables and CRF and to determine potential predictors of clinical outcome variables. Multivariate regression analyses were also performed to determine the correlations between specific variables and CRF. For all analyses, $P < 0.05$ was considered to be statistically significant.

Results

Patient Characteristics

A total of 211 women (mean age 55.2 ± 11.6) completed our questionnaires; the patients had been diagnosed with different types of ovarian cancer. The time duration after treatment ranged from 6 to 151 months (mean duration: 28.0 ± 21.95 months). Analysis showed that 135 patients were menopausal and/or undergoing chemotherapy prior to surgery while 76 were not. The mean level of hemoglobin at baseline was 10.59 ± 1.54 g/dl (Table 1). In total, 26.32% of the recruited patients who had experienced a menstrual period prior to treatment, and 14.07% of patients who were menopausal before treatment, reported severe and moderate cancer-related fatigue following diagnosis with ovarian cancer.

Table 1

Demographic and treatment characteristics ¶measurement date and count date¶

Characteristic\measurement date	Mean	Standard deviation
Age (years)	55.2 (19-87)	11.6
Time since treatment (months)	28 (0-145)	21.5
Number of chemotherapy cycles	5.96	2.91
Hemoglobin level after surgery (g/L)	105.90	15.35
Characteristic\count date	<i>n</i>	%
Had menstrual period before treatment	76	36.02
Menopausal before treatment	135	63.98
Pathological subtype		
Serous carcinoma	108	51.18
Mucinous carcinoma	17	8.06
Other form of carcinoma	86	40.76
Chemotherapy regimens		
Received cisplatin	66	31.28
Received other platinum-based therapy	88	41.71
Received mixed therapy	50	23.69
Received therapy without platinum	7	3.32

We divided the cases into three groups according to the time of treatment. We found that there was no significant difference in CRF score when compared between patients who were treated <12 months ago and those treated >12 months or <24 months ago ($P>0.05$) (Table 1). However, there was a significant difference in CRF score when compared between patients who underwent treatment >24 months ago and those who had been treated <12 months and <24 months ago ($P<0.05$) (Table 2).

Table

The difference of CFS scores between groups with different distance from treatment time

Different Group	P value	p value
Group A	Group B	Group C
	0.53	0.00
Group B	Group A	Group C
	0.53	0.00
Group C	Group A	Group B
	0.00	0.00
Group A Time since treatment $\leq$ 12 months Group B Time since treatment > 12 months and $\leq$ 24 months Group C Time since treatment > 24 months		

Analysis of fatigue

Fatigue was reported in 206 (97.63%) of the 211 completed questionnaires; 39 patients (18.48%) reported severe fatigue, 38 patients (18.09%) reported moderate fatigue, and 1 patient (0.47%), reported severe fatigue. In total, 167 patients reported mild fatigue.

Variables associated with fatigue

Time since treatment

As shown in Table 2, the mean time since treatment across the entire study cohort was 28 months. There was a significant relationship between fatigue and the time since treatment, as determined by linear regression ($t=-6.553$, $P=0.000$). Analysis also showed that the time since treatment was significantly and negatively correlated with CFS score ($P < 0.05$).

Menopause prior to treatment

Univariate analysis showed that the CRF in patients who had experienced a menstrual period prior to treatment was significantly higher than those who had experienced menopause prior to treatment.

Sleep

Linear regression and one-way ANOVA both supported a close association between CFS score and sleep disorders and that patients with sleep disorders were more prone to fatigue ($t=-3.171$, $P=0.002$). Patients with sleep disorders were more prone to fatigue($P<0.05$). (Table 1)

Hemoglobin

Data analysis showed that there was a significant and negative correlation between hemoglobin and CRF ($t=-2.287$, $P=0.023$). (Table 1)

Linear regression and one-way ANOVA of clinical variables and CRF showed that there were no significant correlations between CRF and age, the number of chemotherapy cycles, the type of chemotherapy regimen, and the pathological subtype.

To further analyze the potential association between clinical variables and CRF, we performed multivariate linear regression analysis. Significant correlations were detected between CRF and age ($t=3.251$, $P=0.001$), time since treatment ($t=-6.258$, $P=0.000$), menopause prior to treatment ($t=4.056$, $P=0.000$), and sleep disorders ($t=-0.318$, $P=0.008$). (Table 3) There was no significant correlation between CRF and the number of chemotherapy cycles, chemotherapy regimens, pathological subtype, and hemoglobin level after operation.

Table 3

Linear regression and one-way ANOVA of clinical variables and CRF

Clinical variables	<i>t</i>	<i>P</i>
Ages (years)	-0.218	0.827
Number of chemotherapy cycles	1.174	0.242
Time since treatment	-6.553	0.000
Chemotherapy regimens	0.804	0.422
Pathological subtype	-1.087	0.278
Hemoglobin level after operation	-2.287	0.023
Menopausal before treatment (or not)	2.650	0.009
Sleep disorders (or not)	-3.171	0.002

Table 4

Multiple linear regression and one-way ANOVA of clinical variables and CRF

Clinical variable	Beta	<i>t</i>	<i>P</i>
Age (years)	0.284	3.251	0.001
Number of chemotherapy cycles	0.130	1.920	0.056
Time since treatment	-0.393	-6.258	0.000
Chemotherapy regimens	-0.020	-0.318	0.751
Pathological subtype	-0.047	-0.761	0.447
Hemoglobin after operation	-0.083	-1.324	0.187
Menopausal before treatment (or not)	0.346	4.056	0.000
Sleep disorders (or not)	-0.168	-0.318	0.008

Discussion

Patients who experience a sudden loss of ovarian function as a result of surgery experience more severe CRF. Our main finding was that 97.63% of the patients recruited in this study reported fatigue; of these, 18.48% of women reported severe and moderate CRF following treatment for ovarian cancer. Ovarian cancer is the eighth most common form of cancer to affect women worldwide. The incidence of this condition varies markedly around the world. Previous studies have reported that 80–96% of patients undergoing chemotherapy for cancer complain of CRF [5]. The form of treatment used for ovarian cancer depends on the stage and type of cancer, and includes surgery, chemotherapy, radiation, targeted therapy, hormone therapy, and immunotherapy [6]. CRF is one of the main factors that can influence the quality of life of patients following cancer treatment. Research has shown that CRF may persist for years after chemoradiation therapy and can significantly impair both the quality of life (QoL) and treatment outcome [7].

In our study, we found that patients who had undergone surgery prior to menopause could become fatigued more easily than patients who received surgery after menopause. The CRF score in patients who had experienced a menstrual period prior to treatment was significantly higher than patients who became menopausal before undergoing treatment. We identified a significant association between menopausal symptoms and fatigue within 1 and 2 years of treatment.

It is possible that CRF may be related with sudden changes in the levels of sex hormones. Most ovarian cancers are treated with platinum-based and multi-cycle forms of chemotherapy. Furthermore, the standard treatment for ovarian cancer includes removal of the ovaries prior to chemotherapy [8]. Research has also shown that the removal of both ovaries in premenopausal women with gynecological cancer can result in a series of menopausal symptoms, including hot flashes, emotional disorders, sleep disturbances, and sexual dysfunction; collectively, these factors can exert significant effect on the quality of life (QoL) [9].

A series of scientific experiments, involving rodent models, have proved strong evidence to support the ability of androgenic and estrogenic sex hormones to augment the activation of satellite cells and modulate inflammatory dynamics during the regeneration of muscles. It is possible that humans may adopt a similar mechanism, although this has yet to be proven.

Research has also shown that the iatrogenic symptoms of menopause are usually considerably more severe in comparison to those following a naturally occurring menopause and might adversely affect the QoL in young females who have survived cancer [10]. Premenopausal women undergoing treatment for ovarian cancer can benefit from hormone replacement therapy (HRT); however, there is a lack of consensus with regards to the safety of HRT when administered to this particular group of patients [9]. The Swedish National Guidelines for ovarian cancer recommend that women with iatrogenic symptoms of menopause after undergoing primary treatment for epithelial ovarian cancer can be treated with HRT without any known risk of disease recurrence or reduced survival [11]. HRT has also been reported to improve the QoL in patients with ovarian tumors, although the precise relationship between HT and CRF has yet to be investigated. It therefore appears that the positive effects of HRT in maintaining the QoL outweighs the doubt that exists with regards to the increased risk of recurrence. Thus far, very few studies have investigated the effect of HRT after surgery in patients with epithelial ovarian cancer; furthermore, these existing studies have led to contradictory conclusions [12]. Some scholars suggest that HRT is associated with angiogenesis and may stimulate residual ovarian cancer cells or visible disease in women receiving EOC, or induce new hormone-dependent diseases, such as breast cancer.[9]

As treatment options are improving, the life expectancy of patients with ovarian cancer are beginning to improve; outcomes related to QoL are therefore very important. HRT can relieve menopausal symptoms in women with early-stage ovarian cancer and improve the QoL of those with advanced stages of the disease [13]. Due to the sudden fall in hormone levels caused by the removal of the ovaries, the risks associated with premature menopause, including osteoporosis, cardiovascular disease, venous thromboembolic disease, and stroke, may outweigh the risk of using HRT [14].

We found that the fatigue caused by chemotherapy reached maximal levels within the first two years of treatment but then began to decline. One notable finding from baseline evaluations was the profound difference in the level of fatigue experienced by patients and controls. Previous studies have suggested that fatigue can remain a significant problem for several years following chemotherapy. We observed clear improvement in the fatigue experienced by our patients over the two years of follow up; this finding supported previous work and was reassuring, although patients remained more fatigued than controls when tested two years after chemotherapy. Cognitive dysfunction, menopausal symptoms, and fatigue are important adverse effects of chemotherapy but improve slowly over the following two years in most patients. In addition, fatigue has been found to co-exist with inflammation-associated anemia caused by a reduction in iron levels in response to thyroid insufficiency or the impaired function of the IL-6-mediated the hypothalamic-pituitary-adrenal axis [15].

The clear interaction between fatigue and menopausal symptoms raises the possibility that nocturnal vasomotor symptoms interfere with the quality or duration of sleep. In our study cohort, we found that CRF and cancer-related sleep disorders were positively correlated with fatigue. Most studies in this area found that sleep disorders were more severe in fatigued than non-fatigued patients, and also that sleep disorders were a significant predictor of fatigue. A recent meta-analysis of cross-sectional data from 24 studies reported a higher odds of experiencing sleep disturbance in perimenopause (1.60), postmenopause (1.67), and surgical menopause (2.17) when compared to premenopausal women [16]. In another study, Savard and Morin reviewed the epidemiology of insomnia in patients with cancer and concluded that insomnia created an additional risk for intense and persistent fatigue following cancer treatment. Other investigators have suggested that CRF and sleep disorders should be considered as a clinical syndrome [17]. Another study reported that increasing levels of follicle stimulating hormone (FSH) were associated with a greater odds of waking up several times during the night, and that decreased levels of estrogen were associated with a higher odds of difficulty falling asleep and staying asleep [18]. Consequently, it is evident that sleep quality can be affected by hormonal changes and result in increased levels of fatigue. Moreover, several recent reviews have indicated that a strong inter-relationship exists between sleep disorders and CRF and that the strength of this association changes with differing times of diagnosis and treatment .

In the present study, we carried out linear regression analysis and identified a negative correlation between hemoglobin level and CRF but failed to identify any such significant correlation between these factors in our multivariate linear regression analysis. Anemia appears to be particularly prevalent in cancer patients receiving surgery and chemotherapy. This form of anemia is multi-factorial but is sustained in part by concurrent chemotherapy and the relative deficiency in endogenous erythropoietin that is associated with chronic disease [19]. However, it is well known that anemia is one of the main factors responsible for fatigue in patients with cancer. In a previous study, Littlewood et al. reported that hemoglobin concentrations were associated with improvements in fatigue and that patients achieving a 2g/dl increase in the level of hemoglobin also showed improvements in the FACT fatigue subscale; patients who did not achieve a change in hemoglobin level experienced a decline in the fatigue subscale [20]. Our study found no significant difference in CRF when compared between patients receiving different platinum-based chemotherapy regimens. The mechanism underlying chemotherapy-induced fatigue has yet to be elucidated in detail. However, it is evident that the energy supply to cells will decrease if there are disruptions in the structure and function of mitochondria [21, 22]. Research involving patients receiving chemotherapy has demonstrated that chemotherapy always targets the skeletal musculature in a non-specific manner, particularly, the mitochondria; inevitably, this will induce adverse side effects due to low energy supply and high levels of oxidative stress [23]. Mitochondrial dysfunction plays a major role in the development of diseases associated with energy metabolism. It has also been established that impaired energy production, or the longitudinal depletion of ATP, induces increased levels of physical disability, such as that observed in CRF or chronic fatigue syndrome (CFS).

Previous researchers proposed that chemotherapy drugs such as oxaliplatin competitively substitute copper (Cu^{2+}) on the copper transporter 1 (CT1) protein, thus reducing the transportation of Cu^{2+} and

leading to a reduction in the mitochondrial pool of Cu^{2+} . The mitochondrial Cu^{2+} pool is known to be critical for the function of complex IV and COX17 as well as oxidative phosphorylation [24].

Patients treated extensively with chemotherapy have reported a lower QoL, increased levels of fatigue, and less vigor, when compared with patients with earlier stages of disease and receiving less-intensive treatments.

This study has certain limitations that need to be considered. First, this is a retrospective study; our findings should be confirmed in larger prospective study. Secondly, our study lacked interventions to verify the specific factors associated with CRF. Finally, none of our patients were treated with HRT.

Conclusion

Our analysis indicated that changes in the levels of sex hormones may exert influence on the prognosis of CRF in patients with ovarian cancer. However, our findings need to be validated in future prospective studies involving a larger sample size. It is also necessary to identify the specific mechanisms underlying these relationships.

Declarations

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