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CHEMOTHERAPY-INDUCED CANCER-RELATED FATIGUE IN CERVICAL AND BREAST CANCER SURVIVORS: A CROSS-SECTIONAL STUDY IN SURABAYA, INDONESIA

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Abstract - Cervical and breast cancers are the two top leading cases of female cancer worldwide. Both cases' regiments usually involve chemotherapy to some extends. One of the side effects of chemotherapy usage in cancer management is the occurrence of cancer-related fatigue (CRF) resulted in impaired quality of life. This study aimed to analyze the effect of chemotherapy on CRF in cervical and breast cancer survivors. This cross-sectional study involved 41 and 26 cervical and breast cancer survivors respectively, in the district of Rangkah, Gading, and Pacarkeling, Surabaya, Indonesia. Instrument of Fatigue Symptom Inventory (FSI) was used in data collection. Independent sample T test, Mann-Whitney U test, and linear regression test were used in data analysis ($\alpha < .05$). Results showed that most respondents undertook chemotherapy only or in combination with surgery and radiotherapy (@32.8%). As a side effect, most respondents experienced mild fatigue (64.2%). Regimen for both cases was not significantly different ($p = .076$), but CRF level between both cases was significantly different ($p = .009$). Chemotherapy has no significant effect on CRF both in cervical and breast cancer survivors ($p = .060$ and $p = .784$ respectively). Other potential factors possibly play a more important role in determining CRF level in both cases, such as cancer symptom, malnutrition, infection, comorbidity, psychological and emotional distress.

Index Terms - Breast cancer, cervical cancer, chemotherapy, cancer-related fatigue.

I. INTRODUCTION

Cancer is the growth of new cells that form abnormal tissue and characterized by uncontrolled function [11]. A study in 187 countries from 1980 until 2010 was conducted to analyze the epidemic of cervical and breast cancer incidence and mortality worldwide. Global breast cancer incidence increased from 641,000 (95% uncertainty intervals 610,000–750,000) cases in 1980 to 1,643,000 (1,421,000–1,782,000) cases in 2010, an annual rate of increase of 3.1%. Global cervical cancer incidence increased from 378,000 (256,000–489,000) cases per year in 1980 to 454,000 (318,000–620,000) cases per year in 2010—a 0.6% annual rate of increase. Breast cancer killed 425 000 (359,000–453,000) women in 2010, of whom 68,000 (62,000–74,000) were aged 15–49 years in developing countries. Cervical cancer death rates have been decreasing but the disease still killed 200,000 (139,000–276,000) women in 2010, of whom 46,000 (33,000–64,000) were aged 15–49 years in developing countries. More policy attention is needed to strengthen established health system responses to reduce breast and cervical cancer, especially in developing countries [6]. In 2008, Indonesia's death rate from cancer was 245 per 100,000 inhabitants (men > women); in which lung cancer being the most frequent killer, followed by breast and colon cancer (WHO, 2008) [22]. It can be estimated that the incidence of cancer in Indonesia is 0.1% of the population, and more than 50% of cancer patients firstly come to seek for medication in an advanced stage [22]. In 2014, the incidence of breast

cancer occupies the first position, followed by cervical cancer with the number of 20,928 cases in Indonesia [26]. In the period of six years we can see that more women suffered from cancer in Indonesia.

In general, cancer therapy includes surgery, chemotherapy and radiotherapy. Chemotherapy is a therapy that involves the use of chemicals or drugs that aim to kill cancer cells [15]. The hybrid model suggests that cancer-related stressors and cancer therapies cause a decrease in four major areas, such as cognitive function, nutrition, muscle strength, and sleep quality, affecting the ability to adapt to ill conditions; where changes in the biological, psychological, and functional aspects result in CRF [14]. The negative impact of CRF can even be felt before the formal diagnosis of cancer established, and continues to be experienced during the treatment process. CRF has significant impact on health status [1]. CRF is subjective, which can affect physical and cognitive function, psychosocial, and can reduce QOL [10]. The National Comprehensive Cancer Network (2015) defines CRF as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [23]. Although subjective CRF is often related to objective changes in physical functioning or impaired performance status, the two phenomena are not synonymous and need to be distinguished. The underlying mechanisms and pathophysiology of CRF are unclear [19]. Pathobiology of CRF is very complicated, and is caused by a cascade of events that

result in the production of proinflammatory cytokines, HPA activation dysfunction, endocrine and/or metabolic dysregulation, circadian rhythm disorders, and neuromuscular function abnormalities [17].

CRF is a symptom that is often experienced by the majority of cancer patients, especially those who undergoing chemotherapy or radiation therapy [4]. Oppositely, Jean-Pierre, et al. (2007) stated that CRF is not affected by the type of cancer, nor the type of therapy that is undertaken [10]. There is still a debate in the fields about whether the use of chemotherapy causes fatigue/CRF in cancer patients or not. This study aimed to analyze the effect of chemotherapy on CRF, especially in cervical and breast cancer survivors.

II. METHOD

A. Design and Ethic

This is a cross-sectional study in which no follow-up was conducted. Data were obtained at one time. Prior to study, the protocol has been reviewed by the ethical committee of Faculty of Nursing, Universitas Airlangga, Surabaya, Indonesia (ethical clearance certificate number: 681-KEPK).

B. Sample

Population was all cervical and breast cancer survivors in the district of Rangkah, Gading, and Pacar Keling, Surabaya (N=105). Inclusion criteria was adult (> 18 years old), cancer diagnosis has been confirmed by authorized health center, chemotherapy was being one of the regiment, and regularly home-visited by a palliative volunteer under the supervision of Rangkah Public Health Center, Surabaya, Indonesia. Exclusion criteria were bad physical/psychological condition, disorientation, impaired consciousness, and rejection on filling out the consent form. Total sampling was applied and sample size of 67 was obtained: 41 and 26 cervical and breast cancer survivors respectively.

C. Instrument

Questionnaire of demography (self-developed) and Fatigue Symptom Inventory (FSI) developed by Moffitt Cancer Center and University of South Florida (1998) were used for collecting data [9]. Therapy or regiment was coded into six categories: 1 = chemotherapy only, 2 = surgery + chemotherapy, 3 = chemoradiotherapy, 4 = surgery + chemoradiotherapy, 5 = surgery + chemoradiotherapy + analgesic, and 6 = surgery + chemoradiotherapy + oral medicine (other than analgesic). FSI consists of four domains spread in 14 items of fatigue self-assessment: severity (4 items), frequency (2 items), diurnal variation (1 item), and impact on quality of life (7 items). Total score of FSI was categorized into three levels of CRF: mild,

moderate, and severe CRF by total score of 0-44, 45-88, and 89-134 respectively. Data were then analyzed by independent sample T test, Mann-Whitney U test, and linear regression test ($\alpha < .05$).

III. RESULTS

There were 41 and 26 cervical and breast cancer survivors participated in this study. Table 1 explains the demographic characteristics of study respondents. Most respondents are married woman, 51-60 years old, housewife, Islam, Javanese, high school graduates, lives with spouse, and Gross Domestic Product (GDP) less than minimum wage of Surabaya in 2018 (IDR 3.2 million). These results indicate that majority of cervical/breast cancer suffered by late adult women with lower middle socioeconomic status. Table 2 explains primary data related to cancer diagnosis and regiments/treatment. Most respondents were diagnosed with cancer before 2014. This fact indicated that the survival rate of both cases is particularly long, which makes them a chronic disease with high burden and requires long-term supportive care. Table 3 explains the CRF level in both cases. Most respondents experienced mild fatigue (64.2%). Result of Mann-Whitney U test showed that therapy of cervical and breast cancers was not significantly different ($p = .076$), but result of independent T test showed that CRF level was significantly different between survivors of cervical and breast cancers ($p = .009$) especially in item 11 and 13 of FSI about CRF-induced mood disorder and frequency of CRF occurrence per day respectively ($p = .025$ and $p = .011$ respectively). There was a big possibility that CRF in both cases was not induced by chemotherapy. Result of linear regression test confirmed that overall therapy was not significantly influenced CRF in cervical and breast cancer survivors ($p = .432$). Specific linear regression in each case showed that chemotherapy has no significant effect on CRF with $p = .060$ and $p = .784$ for cervical and breast cancer respectively.

IV. DISCUSSION

Results showed that chemotherapy has no significant effect on CRF, both in cervical and breast cancer survivors. This fact was obtained potentially because the therapy of both cases was not significantly different, but CRF level was found to be significantly different between cases. This study result was supported by Jean-Pierre et al. (2007) who stated that CRF is not affected by the type of cancer, nor the type of therapy that is undertaken [10]. Minton, et al. (2012) also found that there was no correlation between demographic characteristic and therapy with CRF [13]. Generally, therapy of cancer includes surgery, chemotherapy, and radiotherapy. In early

stage, surgery is highly recommended than other types of therapy, but oppositely for the advanced stage. Surgery in advanced stage was done for palliative purposes: increasing quality of life by alleviating disturbing symptoms and increasing life functioning. The usage of chemotherapy in advanced stage was preferred because of its systemic effect, compare to the local effect of surgery and radiotherapy. But, its usage

also induced many side effects, such as severe nausea and vomiting resulted in malnutrition, hair loss (alopecia) and darken/dry skin resulted in impaired body image, increases of pain intensity and risk of infection, diarrhea, stomatitis, neuropathy, myalgia, tasting change, and trombositopenia [15].

Table 1: Demographic Characteristic

CHARACTERISTIC	CERVICAL CANCER (n=41)		BREAST CANCER (n=26)	
	FREQUENCY	%	FREQUENCY	%
1. Age (years old)				
a. 21-30	0	0	1	3.85
b. 31-40	4	9.76	8	30.77
c. 41-50	8	19.51	6	23.08
d. 51-60	15	36.59	5	19.23
e. 61-70	13	31.71	4	15.38
f. > 70	1	2.44	2	7.69
2. Religion				
a. Catholic	0	0	1	3.85
b. Christian	7	17.07	5	19.23
c. Islam	34	82.93	20	76.92
3. Ethnic				
a. Javanese	34	82.93	25	96.15
b. Maduranese	6	14.63	0	0
c. Chinese	1	2.44	1	3.85
4. Educational background				
a. Primary school	15	36.59	5	19.23
b. Secondary school	12	29.27	1	3.85
c. High school	9	21.95	13	50.00
d. Diploma / Bachelor degree	2	4.88	7	26.92
e. Uneducated	3	7.32	0	0
5. Marital status				
a. Single	2	4.88	3	11.54
b. Married	35	85.37	18	69.23
c. Widow	4	9.76	5	19.23
6. Living at home with				
a. Spouse	35	85.37	14	53.85
b. Children	16	39.02	17	65.38
c. Alone	2	4.88	0	0
d. Parents	0	0	4	15.38
e. Sibling	0	0	1	3.85
7. Occupational status				
a. Full-timer	2	4.88	4	15.38
b. Part-timer	3	7.32	2	7.69
c. Retired	0	0	4	15.38
d. Housewife	34	82.93	16	61.54
e. Unemployed	2	4.88	0	0

8. GDP per month				
a. Less than minimum wage	31	75.61	11	42.31
b. Minimum wage – IDR 5 million	5	12.20	6	23.08
c. More than IDR 5 million	3	7.32	5	19.23
d. No income	2	4.88	4	15.38

Table 2: Primary Data

CHARACTERISTIC	CERVICAL CANCER (n=41)		BREAST CANCER (n=26)	
	FREQUENCY	%	FREQUENCY	%
1. Firstly diagnosed				
a. 2018	0	0	1	3.85
b. 2017	5	12.20	7	26.92
c. 2016	10	24.39	4	15.38
d. 2015	5	12.20	4	15.38
e. 2014	5	12.20	2	7.69
f. < 2014	16	39.02	8	30.77
2. Type of therapy				
a. Chemotherapy	13	31.71	9	34.62
b. Surgery + chemotherapy	2	4.88	11	42.31
c. Chemotherapy + radiotherapy	7	17.07	1	3.85
d. Surgery + chemotherapy + radiotherapy	17	41.46	5	19.23
e. Surgery + chemotherapy + radiotherapy + analgesic	1	2.44	0	0
f. Surgery + chemotherapy + radiotherapy + medicine	1	2.44	0	0

Table 3: CRF Level

CHARACTERISTIC	CERVICAL CANCER (n=41)		BREAST CANCER (n=26)	
	FREQUENCY	%	FREQUENCY	%
1. Mild	31	75.61	12	46.15
2. Moderate	9	21.95	11	42.31
3. Severe	1	2.44	3	11.54

Although therapy has no significant effect on CRF, but we could see from Table 2 that most breast cancer survivors undertook surgery plus chemotherapy regimens, while cervical cancer survivors undertook that regimens also but plus radiotherapy (more complex). The complexity of therapy was determined by cancer progression, individual condition, preferences/perception, and other subjective factors involve both physicians and the patients. CRF is one of the most common symptoms reported by patients and is defined as the feeling of extraordinary exhaustion associated with a high level of distress, disproportionate to the patients' activity, and is not relieved by sleep or rest [25]. Prevalence rates range from 59 to nearly 100% depending on the clinical status of the cancer. At present, the etiology of CRF is poorly understood and the relative contributions of the

neoplastic disease, various forms of cancer therapy, and comorbid conditions remain unclear. In any individual, the etiology of CRF probably involves the dysregulation of several physiological and biochemical systems. Mechanisms proposed as underlying CRF include 5-HT neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and ATP metabolism, HPA axis dysfunction (hypothalamic–pituitary–adrenal pathway), circadian rhythm disruption, and cytokine dysregulation. Currently, these mechanisms are largely based on evidence from other conditions in which fatigue is a characteristic, in particular chronic fatigue syndrome and exercise-induced fatigue [16].

Borneman (2013) proposed some factors that potentially influence CRF other than therapy, such as cancer symptoms (physically and psychologically),

comorbidity in various body systems, and infection [4]. Physical cancer symptoms which could induce CRF e.g. pain, shortness of breath, inability to perform daily tasks, palpitations, insomnia, lack of appetite, and immobility; while the psychological symptoms include depressed mood, anxiety, and emotional distress. Borneman statements was confirmed in the previous study of Minton, et al. (2012) towards 105 breast cancer survivors with CRF by results of there was a significant correlation found between pain, insomnia, anxiety, and depression with CRF [13]. Comorbidity refers to not only organ function failure which includes cardio, renal, pulmo, nerve, digestive, liver, and endocrine [4]; but also anemia, cachexia, sleep disorders, and depression [16]. Increased risk of infection in cancer patients could happen because of poor protein and caloric intake post-chemotherapy due to its side effects of nausea and vomiting resulted in low immunity [12, 21]. In cancer patients, nutrients can affect tumor biology, comorbidity and therapeutic response [1]. Weight loss and nutritional problems are often associated with cancer [18]. Cancer in the body and therapy undertaken by cancer patients make nutrition problems worsen [7, 20]. CRF is an important symptom in cancer and has been shown to be associated with psychological and emotional distress [3, 5]. Low immunity related to increase risk of infection in cancer patients could be a result of psychological distress also. Depression, anxiety, and stress are associated with cancer. Stress, anxiety, and depression have been found to depress the immune system. Depression and stress have also been found to create inflammatory changes in the body and there is emerging evidence that inflammation is involved in cancer pathogenesis and in CRF [24]. CRF in breast cancer was significantly different from CRF in cervical cancer in this study context. We could find more mild to moderate CRF in breast cancer compare to most mild CRF in cervical cancer respondents (Table 3). After deeper analysis using independent T test, it was found that those significant differences caused by CRF-induced mood disorder and CRF occurrence per day. Most respondents of breast cancer experienced mild mood disorder (50%) and low occurrence of CRF per day (61.54%), while most respondents of cervical cancer experienced mild mood disorder (75.61%) and low occurrence of CRF per day (85.37%). Mood is a person's subjective emotional state. According to the DSM-IV the term mood disorder is used for a group of diagnoses where the primary symptom is a disturbance in mood, or in other words the experience of an inappropriate, exaggerated or limited range of feelings. Mood disorders are common in patients with cancer which probably cause by an imbalance in neurotransmitters [8]. CRF syndrome in disease free breast cancer survivors has a significant effect on mood disorder [2]. The mood

disorder can be triggered by the cancer diagnosis on its own, or it can be treatment-induced in cases where the aetiology can be found in the physiological effect of a psychoactive drug or chemical substance [8]. A study towards 60 breast cancer survivors with CRF compare to 140 breast cancer survivors without CRF showed that there was a significant difference of mood found [2]. Similar study in cervical cancer survivors is not found yet, therefore this condition gives a big chance for upcoming studies in this area. Several common problems are associated with CRF in women with breast cancer, including treatment side effects, obesity, arm/upper quadrant symptoms, sleep disturbances, psychological effects, and comorbid conditions [3]. CRF in cervical and breast cancer survivors could be perceived in many different perspectives by the individuals. FSI used in this study enable cancer survivors to make independent self-assessment about their CRF condition. CRF assessment in cancer patients needs to be done continuously to support early diagnosis and treatment of CRF, so that optimum quality of life could be assured. This study has some limitations also. The nature of cross-sectional study with a single time point data collection has made the pattern, consistency, and intensity of CRF value over time was not assessed. Future study needs to incorporate a longitudinal cohort design to improve the present research methodology. Other than study design, weakness also presents in the instrument. FSI does not consider subjective value, such as culture, habit, and other individual background, but being used to assess something subjective like CRF. There is a possibility that the judgements of respondents influenced by not only physical condition related to cancer and its treatment, but also specific individual value or preferences.

CONCLUSION

There was a significant difference of CRF between cervical and breast cancer survivors, especially the aspects of CRF-induced mood disorder and the frequency of CRF occurrence per day. Regiments of cervical and breast cancer was not significantly different. Chemotherapy has no significant effect on CRF in cervical and breast cancer survivors. Other potential factors possibly play a more important role in determining CRF level in both cases, such as cancer symptom, malnutrition, infection, comorbidity, psychological and emotional distress.

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