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CANCER ANOREXIA CACHEXIA SYNDROME IN PATIENTS WITH CARCINOMA AT PROF. DR. R. D. KANDOU HOSPITAL MANADO

Haroen H. Rotty L^{1*}, Lasut P¹, Hendratta C¹, Balansa E¹, Harlinda Harun¹

¹Medical Oncology Hematology Division, Department of Internal Medicine
Faculty of Medicine, University of Sam Ratulangi, Prof.Dr.RD Kandou Hospital, Manado.

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*Correspondence to Author:

Haroen H. Rotty L
Medical Oncology Hematology
Division, Department of Internal
Medicine. Faculty of Medicine,
University of Sam Ratulangi,
Prof.Dr.RD Kandou Hospital,
Manado.

E-mail:

linda_rotty@yahoo.com

ABSTRACT

BACKGROUND : Carcinoma is a malignant disease caused by uncontrolled cell proliferation and the loss of normal apoptosis of the cells cycle. The most common nutritional problems in patients with carcinoma is cancer anorexia-cachexia syndrome (CACS), characterized by weight loss, and asthenia. Etiology of this syndrome remains unclear but probably multifactorial. This study was aimed to determine the incidence of CACS in carcinoma patients before and after they underwent chemotherapy.

METHODS: A retrospective cohort study design with descriptive analytic method. 206 carcinoma patients undergoing chemotherapy at Prof. dr. R. D. Kandou hospital from February to August 2016 as subject of this research and met the inclusion criteria, namely carcinoma patients who had completed chemotherapy cycle for 6 months was included in this study. Cancer anorexia cachexia syndrome was assessed using Scored Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire and anthropometry examination and then grouped into A (good nutritional status), B (pre cachexia) and C (cachexia). All patients included in this study were assessed when undergoing chemotherapy for the first time and 6 months after.

RESULTS: A total of 206 patients were included in this study. Most were breast (39,30%), ovarium (18,44%) and cervix (15,53%) carcinomas. The most common stages before they underwent chemotherapy were stage IIb (breast carcinoma), IIIa (ovarian carcinoma) and IIIa (cervical carcinoma). The most

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common comorbidities were type 2 DM, lung disease and kidney disease from each of the three groups. The incidence of CACS was as follows: breast carcinoma before chemotherapy; A (n = 51, 62.96%), B (n = 30, 37.04%) and after chemotherapy; A (n = 73, 90.12%) and B (n = 8, 9.88%). Ovarian carcinoma before chemotherapy; A (n = 14, 36.84%), B (n = 20, 52.63%), C (n = 4, 10.53%) and after chemotherapy; A (n = 16, 42.11%), B (n = 22, 57.89%). Cervical carcinoma before chemotherapy; A (n = 14, 43.75%), B (n = 10, 31.25%), C (n = 8, 25.00%) and after chemotherapy; A (n = 18, 56.25%), B (n = 12, 37.50%) and C (n = 2, 6.25%). In the breast carcinoma group prior to chemotherapy there was a very significant relationship between CACS events with stage ($p < 0.000$) and with coexisting disease ($p < 0.000$). In the ovarian carcinoma group prior to chemotherapy there was a significant relationship between CACS events with stage ($p = 0.028$) and with coexisting disease ($p = 0.038$). In the cervical carcinoma group prior to chemotherapy there was no correlation between CACS events with stage ($p = 0.143$) and also with coexisting disease ($p = 0.094$).

CONCLUSION: In this study, visible improvements in nutritional status of carcinoma patients after underwent chemotherapy for 6 months. There is a significant association between the occurrence of CACS with the stage and the presence of comorbidities in breast and ovarian carcinoma group prior to chemotherapy. In cervical carcinoma group there was not a statistically significant relationship of CACS with stages, but the incidence was more common in patients with advanced stage and comorbidities.

INTRODUCTION

Carcinoma is a malignant disease caused by uncontrolled cell proliferation and loss of normal apoptosis of the cell cycle.¹ Nutritional problems always found in almost all cancer patients, often seen as one of the important signs of cancer, such as cancer anorexia cachexia syndrome (CACS) which is common cause of death for cancer patients. Cancer anorexia-cachexia syndrome (CACS) is a condition characterized by symptoms of weight loss, anorexia and shrinking of muscle mass, the etiology of this syndrome remains unclear but probably multifactorial. The cause of cachexia in cancer were divided into three groups: anorexia due to malignancy, treatment and metabolism disorders.² This study was aimed to determine the incidence of CACS in carcinoma patients before and after they underwent chemotherapy.

METHODS

This study used a retrospective cohort study design with analytic descriptive method. 206 subjects of carcinoma patients underwent chemotherapy in Prof. dr. RD Kandou Hospital from February to August 2016 and met the inclusion criteria, namely carcinoma patients and have completed a cycle of chemotherapy for 6 months was included in this study. Cancer anorexia cachexia syndrome was assessed using Scored Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire and the examination of anthropometry, all subjects were then grouped into A (good nutritional status), B (moderately malnourished or pre-cachexia with weight loss $\leq 5\%$ in 1 month or 10% in 6 months) and C (severe malnutrition or cachexia with weight loss $> 5\%$ within 1 month or $> 10\%$ in 6 months) categories. All patients included in this study were assessed when undergoing chemotherapy for the first time and 6 months after.

RESULTS

206 subjects included in this study were as follows; breast carcinoma (n = 81, 39.30%); ovarian carcinoma (n = 38, 18.44%); cervical carcinoma (n = 32, 15.53%); nasopharyngeal carcinoma (n = 12, 5.82%); (n = 6, 2.91%), for each of colon and tongue carcinoma; (n = 4, 1.94%), for each of lung and thyroid carcinoma (n = 4, 1.94%); (n = 3, 1.45%), for each of osteosarcoma, prostate, rectal and endometrial carcinoma; (n = 2, 0.97%), for each of mandible carcinoma and choriocarcinoma; and (n = 1, 0.48%) for each of retinoblastoma adenocarcinoma of the oesophagus, sarcoma, cardiac carcinoma. Overall, the most common carcinomas were carcinoma of the breast, ovary and cervix and most common stagings obtained when first diagnosed were IIb (breast carcinoma), IIIa (ovarian carcinoma) and IIIa (cervical carcinoma), respectively, while most common comorbidities were type 2 DM, lung disease and kidney disease. Incidence of CACS were as follows; in breast carcinoma before chemotherapy, A (n = 51, 62.96%), B (n = 30, 37.04%) and after chemotherapy A (n = 73, 90.12%) and category B (n = 8, 9.88%); in ovarian carcinoma before chemotherapy, A (n = 14, 36.84%), B (n = 20, 52.63%), C (n = 4, 10.53%) and after chemotherapy, A (n = 16, 42.11%), B (n = 22, 57.89%); in cervical carcinoma group before chemotherapy, A (n = 14, 43.75%), B (n = 10, 31.25%), C (n = 8, 25.00%) and after chemotherapy, A (n = 18, 56.25%), B (n = 12, 37.50%) and C (n = 2,

6.25%). In the breast carcinoma group prior to chemotherapy there was a very significant relationship between CACS events with stage ($p < 0.000$) and with coexisting disease ($p < 0.000$). In the ovarian carcinoma group prior to chemotherapy there was a significant relationship between CACS events with stage ($p = 0.028$) and with coexisting disease ($p = 0.038$). In the cervical carcinoma group before chemotherapy there was no correlation between CACS events with stage ($p = 0.143$) and also with coexisting disease ($p = 0.094$).

DISCUSSION

Carcinoma is a malignant disease caused by uncontrolled cell proliferation and the loss of normal apoptosis of the cells cycle.¹ Nutritional problems are common in patients with cancer anorexia-cachexia syndrome (CACS), characterized by symptoms of weight loss, anorexia and asthenia, the etiology of this syndrome remains unclear but probably multifactorial.²

In this study, three groups with the highest incidence were breast carcinoma, ovarian carcinoma, and carcinoma of the cervix that were in accordance with the data from Riskesdas 2013 which states that the prevalence of carcinoma in women tend to be higher than men. This is because women are usually more concerned about their health compared to men, therefore more cases of carcinoma are detectable in women.³ This was also supported by 2014 data from the Health Ministry of RI which states that the highest incidence of carcinoma in women are breast and cervical carcinoma, while in men are lung and colorectal carcinoma.⁴

Based on the results of the bivariate analysis using Chi-square test, there was a significant association between the occurrence of CACS with the stadium in which patient underwent chemotherapy for the first time and the presence of comorbidities in breast and ovarian carcinoma, the more advanced the stages of carcinoma and the presence of comorbidities the higher incidence of CACS. Patients are usually looking for treatment when they are already at an advanced stage because at early stage it is often asymptomatic and patients were unaware of this condition. This is consistent with Suryapratama's statement that cachexia incident in carcinoma patients will be higher in accordance with the increased stage of the disease.⁵

Various aetiopathogenesis are proposed by hematology-oncology experts to explain this condition. A central signal to the body to affect hunger in the arcuate nucleus of hypothalamus, which physiologically are simultaneous interaction between agouti-related peptide (AgRP) neurons and neuropeptide-Y (NPY) that

orexigenic with pro-opiomelanocortin neurons (POMC) and cocaine amphetamine-regulated transcript (CART) peptide that anorexigenic.⁶ In CACS, regulatory interference occurs in the pathway where NPY neuropeptides are inhibited by leptin deficiency in cancer patients with cancer due to decreased appetite.⁷ Inhibition of NPY/AgRP pathway be accompanied by the activation of POMC/CART causing an increase in the stimulation and regulation of α -melanocyte stimulating hormone and corticotrophin releasing hormone that make patients feel full. Various proinflammatory cytokines also play some role in the CACS such as interleukin 1 (IL-1), IL-6, IL-1 β , tumor necrotic factor- α (TNF- α), and interferon- γ (IFN- γ) with various pathomechanism such as the effects of mimicry-inhibition on the hypothalamus, increased proteolysis and damaged proteins miofibrin, reduced MyoD protein as a myogenic transcription factor that modulate the pathways of muscle formation, and increased secretion of nuclear factor- κ B (NF- κ B), which further aggravated the muscle wasting in cancer patients.⁸

Comorbidities also affecting the incidence of CACS. Metabolic disorders in peripheral tissues are exacerbated by comorbidities that have a direct effect on CACS as hypermetabolism which affect carbohydrate, fat and protein metabolisms. Most solid tumors will produce a large amounts of lactic through *Cori* cycle in the liver, this lactate will be converted into glucose (gluconeogenesis) that cancer patients with weight loss has been reported to have an increased liver glucose production up to 40%, which further exacerbate cachexia in carcinoma patients.⁷ In addition to an increase in gluconeogenesis, the CACS will also increase in glycogenolysis and decrease in glycogenesis that in turn will impaired the carbohydrate metabolism.⁸

Insulin resistance that frequently occur in diabetes mellitus is also found in cancer patients that will further deteriorate nutritional problems and increased mortality rates.⁹ This condition occurs due to direct influence of proinflammatory cytokines in insulin action, especially the role of NF- κ B. In insulin-sensitive state, insulin binding to receptors will occur that activate phosphatidylinositol 3-kinase (PI3K) and Akt, where in activation of this pathway will suppress the FoxO activity and caspase-3 and decrease the atrogen-1 and Murf-1, the main enzyme of the ubiquitin-proteosome pathway (UPP), which in turn increasing protein synthesis and decreasing proteolysis. In the state of insulin-resistance the will be a reduction of PI3K activity and inhibition of FoxO and caspase-3, that will increase the expression of UPP component, that lead to loss of muscle mass due to

an increase in proteolysis and decrease in protein synthesis.¹⁰

In contrast to the results of the bivariate analysis between the incidence of CACS with the stage and the presence of comorbidities, in carcinoma of the cervix group this was not statistically significant, maybe due to incidence of CACS in carcinoma of the cervix is more progressive and can occur at an early stage compared to breast and ovary carcinoma. Cervix carcinoma caused by certain types of human papillomavirus (HPV) such as HPV16 and HPV18 which has oncogenes E6 and E7 in which both gene expression is a prerequisite for the development of cancer and malignant phenotype defense. E6 and E7 proteins of HPV will modulate protein that regulates the cells cycle, in which the protein E6 conjugated with a cellular protein called *E6-associated protein* (E6-AP) forming E3 ubiquitin ligase that targets the tumor suppressor p53 degradation. Degradation of p53 will causing the cell not to undergo apoptosis or entering the cell cycle arrest at G1/S. These proteins also induces c-myc protein that can stimulate the telomerase enzyme causing cells to become immortal. E7 protein will bind the hypophosphorilated active form of of p105Rb and family members of the retinoblastoma (Rb) tumor suppressor protein that lead to destabilization and loss of complex PRB / E2F complexes where PRB / E2F serves as a suppressor of the transcription of genes required for cells cycle progression. This will trigger the high metabolism rate of carcinoma cells in cervical carcinoma which affects how cachexia occurs.¹¹

Improvements in the nutritional status carcinoma patients after undergoing chemotherapy for 6 months was found. Worsening events of CACS often occur at the beginning of chemotherapy due to changes in diet patterns such as anorexia or loss of appetite caused by side effects of chemotherapy drugs. Disorders of the tongue may also causing changes in food flavor and aroma which tends to be bitter and therefore affecting the decrease of food intake. Xerostomia, nausea and pain in the throat can diminished the food intake, in the same time defecation disorders such as diarrhea and constipation will affect the absorption of nutrients in the small intestine. If this circumstances can be managed properly it will lessen impact of side effects to chemotherapy patients.¹²

Chemotherapy will actually improve the nutritional status of patients with CACS because optimal chemotherapy will inhibit secretion of proinflammatory factors and procachexia factors such as proteolysis inducing factor (PIF) and lipid mobilizing factor(LMF). By suppressing proinflammatory cytokines such as TNF-

α , IL-1 and IL-6 along with decreasing number of cancer cells improvement in nutritional status in patients with carcinoma will occur, by repairing the carbohydrates, fats and protein metabolism. Tumor necrotic factor- α and PIF is instrumental in increasing in protein degradation and inhibition of protein synthesis. Improvement in neuroendocrine factors primarily on insulin resistance that during the carcinoma process suppressed the anabolic processes will also be seen.¹²

CONCLUSION

There is an improvement in nutritional status of carcinoma patients after undergoing chemotherapy for 6 months. There was a significant association between CACS events with stage and presence of comorbidities in breast and ovarian carcinoma groups before underwent chemotherapy. In cervical carcinoma group there was not a statistically significant relationship of CACS with stages, but the incidence was more common in patients with advanced stage and comorbidities.

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