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Analysis of C-Peptide Levels Among Gynaecological Malignancies Patients Underwent Chemotherapy with Carboplatin Regiment

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ABSTRACT

C-peptide is part of the, which its amounts were equal to endogenous insulin secreted by pancreatic β cells. Carboplatin is one of the chemotherapy regimens that are widely used to treat gynecological malignancies. Carboplatin may cause the damage of β-islets of Langerhans, which may cause defects in insulin synthesis leading to secondary diabetes mellitus or other types of diabetes mellitus. The purpose of this study was to determine the differences in C-peptide, (which reflects endogenous insulin levels) levels in patients with gynecologic malignancy who underwent carboplatin chemotherapy. This study was a comparative observational study with a cross-sectional design. There was a total of 42 subjects who met the inclusion criteria. Subjects with gynecological malignancy post-carboplatin chemotherapy regimens had lower serum C-peptide levels in group II compared to group I. Serum C-peptide levels can further be used to monitor side effects of carboplatin and can be used as a test to diagnose the other types of diabetes mellitus especially before starting the fourth cycle.

Keywords: Carboplatin, C-peptide, gynecological malignancies

INTRODUCTION

Data from WHO shows that there are more than 6 million females diagnosed with gynecological malignancy worldwide and a total of 9 million females died due to the malignancy in the last 2 decades. Gynecological cancers include cervical cancer, ovarian cancer, endometrial cancer, and vulval cancer.[1,2] Medical records from 2017 showed that cervical and ovarian cancer ranks as the 6th and 7th most commonly found the disease in Hasan Sadikin Hospital.[3]

Cancer treatment includes the modalities of surgery, radiotherapy, immunotherapy, and chemotherapy or cytostatic agent. Cytostatics are used in chemotherapy procedures to eliminate or kill cancerous cells. Carboplatin is one of the chemotherapy regimens used in various malignancies, such as endometrial cancer, ovarium cancer, nasopharyngeal cancer, brain cancer, or neuroblastoma. Cisplatin, a derivative of carboplatin, has fewer side effects compared to cisplatin. Carboplatin therapy is given in the cancer patient within six cycles over a period of 21 days.[1,4]

Carboplatin is a Cell Cycle Depending Drugs Non-Specific Phase (CCDD-NSP), which only works on cells in the growing phase. However, it is able to distinguish between normal and cancerous cells, causing normal cells to be affected, which results in some side effects for the patient. One of its possible side effects is beta cell destruction in the pancreas leading to reduced insulin synthesis and secretion, disturbance of blood glucose regulation, and hyperglycemia. Hyperglycemia after the carboplatin regimen contributes greatly to insulin resistance. A state of hyperglycemia after carboplatin is reported in more than 20% of patients with no previous history of diabetes prior to the chemotherapy regimen. The risk of hyperglycemia is also increased after a repeated cycle of carboplatin therapy. Previous research found that the decline of insulin levels begins at the fourth cycle of chemotherapy.[4,5]

One of the laboratory tests to determine the cause of hyperglycemia is the C-peptide test. C-peptide derived in-vivo from proinsulin measures endogen insulin secretion. C-peptide is a preferable and more affordable test compared to insulin since insulin is influenced by external insulin consumption and has a short half-life. Because C-peptide levels are more stable in blood, measurement of C-peptide levels is widely used in daily laboratory practice. Therefore, the C-peptide test together with blood glucose monitoring is important to be performed in gynecologic malignancy patients receiving carboplatin, which induces hyperglycemia.[6-8]

METHODS

This research was conducted from August 2018 to April 2019 using a cross-sectional comparative method with a consecutive sampling method. The subjects are patients diagnosed with gynecological malignancies such as cervical cancer, ovarian cancer, and endometrial or vulval cancer from stage 1 to stage IVC. The subjects also underwent carboplatin chemotherapy in Gynaecological Outpatient Clinic at Hasan Sadikin Hospital, Bandung.

This research measured of C-peptide levels of subjects receiving carboplatin therapy in various cycles. Previous research stated that side effects of carboplatin such as increased urine albumin creatinine ratio, anemia, neutropenia, leukopenia, and hyperglycemia occur after the fourth cycle. Based on statistical analysis, the total population needed was 36 subjects, which were then divided into 2 groups, one group consisted of subjects who underwent chemotherapy in cycles 1-3 and another group consisted of subjects who underwent chemotherapy in cycles 4-6. Clinical data including the cycle of chemotherapy was obtained from history taking and medical record analysis. C-peptide levels were measured with Enzyme-Linked Immunosorbent Assay (ELISA). The reference range for C-peptide in adults is 0.7-1.9 mg/mL. The samples were stored at -20ºC in a freezer until analysis. This research obtained ethical clearance from the Ethical Committee of the Faculty of Medicine, Padjadjaran University with a number of 615/UN6.KEP/EC/2019.

Data collected were then analyzed with Statistical Package for the Social Science (SPSS) version 17. Shapiro Wilk test was used to determine the normality of data. Data with normal distribution would be analyzed with unpaired T-test and data with abnormal distribution would be analyzed with Mann-Whitney test to compare C-peptide levels between subjects from carboplatin therapy in cycle 1-3 and cycle 4-6. Result obtained with a p-value < 0.05 was reported as significant.

RESULTS AND DISCUSSIONS

The subjects of this research were patients diagnosed with gynecological malignancy who visited the Obstetric and Gynaecologic Outpatient Clinic in Hasan Sadikin Hospital that underwent chemotherapy as a treatment of choice for their cancer. During research period, there were 42 subjects who met inclusion criteria and were eligible to participate in this research and signed the informed consent. The characteristics of the research subjects are shown in Table 1.

The data of C-peptide levels were analyzed with the Shapiro-Wilk test to determine the normality of the data. The result of the normality test can be seen in Table 2.

Table 2. Normality test of C-peptide levels

Variable	p-value	Interpretation
C-peptide	<0.005	Abnormal

According to the normality test, it was found that C-peptide levels were not normally distributed; therefore, the data were presented as median. In addition, the comparison of C-peptide levels between both groups in this research was analyzed using the Mann-Whitney test (Table 3).

The subjects in this study were divided into two groups. Group 1 consisted of subjects who underwent the 1^{st} – 3^{rd} cycle of chemotherapy, whereas the second group consisted of subjects who underwent the 4^{th} to 6^{th} cycle of chemotherapy. The median of the first group was 1.03 ng/mL, and the range of the C-peptide level was 0.75 ng/mL–1.46 ng/mL. In addition, the median of the second group

Table 1. Characteristics of research subjects

Variable	First Group (1^{st} – 3^{rd} cycle of Chemotherapy)	Second Group (4^{th} – 6^{th} cycle of Chemotherapy)	p-value
Age (years)			
Mean±SD	49±9	49 ±10	
Cycle			
1-3 (n/%)	19 (45)		
4-6 (n/%)		23 (55)	
Random blood glucose (mg/dL)			
Mean±SD (reference range: <140)	105±12	201±33	**<0.05**
Creatinine clearance (mL/min)			
Mean±SD (reference range: 97-137)	110±29	76±19.6	**<0.05**

Note: SD: Standard of Deviation

Table 3. Comparative measurement of C-peptide level between the first and second group

C-peptide (ng/mL)	First Group (1^{st} – 3^{rd} Cycle of Chemotherapy)	Second Group 4^{th} to 6^{th} Cycle of Chemotherapy	p-value
Median	1.03	0.32	<0.05
Reference range	0.75-1.46	0.05-0.76	

was 0.32 ng/mL and the range of the C-peptide level was 0.05 ng/mL–0.76 ng/mL. The Mann-Whitney test showed a significant difference in C-peptide levels between the first and the second groups. Boxplots of the data from the first and second groups can be seen in Figure 1.

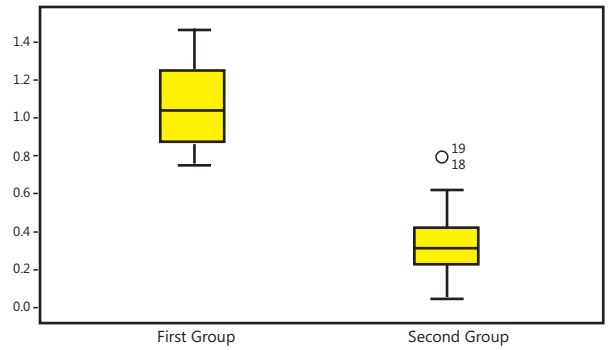

Figure 1. Boxplot of C-peptide level in the first and second groups

Based on the data, it was found that there was a significant increase in random blood sugar levels in the second group. This increase might be caused by the repetitive use of the carboplatin regimen that has already interrupted the homeostasis of blood glucose.

The hyperglycemia condition will benefit the hypoxic cells to obtain another glucose supply. This process will cause bad effects on the patient, such as another oncogenesis and resistance of the cell tumor to the chemotherapy regimen given since this process may result in resistance to apoptotic cells.[8,9]

The carboplatin treatment can lead to the destruction of the microtubule and microfilament in the nephron, thus lowering creatinine clearance from the kidney. Carboplatin therapy is dose-dependent that gives an effect to malignancy patients with kidney function disturbances. If there are significant decreases in creatinine clearance and kidney function, the carboplatin dose should be lowered from the effective dose.[10,11]

From Table 3 and Figure 1, it could be seen that C-peptide levels in the second group were much lower than in the first group. This could be caused by the lowering effect of C-peptide by previous repetitive carboplatin regimen due to its ability to induce the breakdown of the beta-cell Langerhans in the pancreas by modulating the calcium channel membrane at its cell wall, resulting in the dysfunction of beta cells, further mass reduction in whole beta Langerhans cell, and decreased insulin and C-peptide levels.[12,13]

Carboplatin will also stimulate adrenergic by catecholamine and cytokine, which will significantly increase glucagon levels, a primary hormonal mediator from gluconeogenesis. Cytokines such as tumor necrosis factor, IL-1, and catecholamine will independently and synergistically increase hepatic glucose uptake and inhibit the release of insulin from the pancreas to blood. In addition, catecholamine will inhibit insulin attachment with its transporter, thus worsening blood glucose homeostasis.[14-16] This study found that a decrease of C-peptide levels was significant in the second group (after the fourth cycle of chemotherapy); therefore, clinical and glucose monitoring together with a measurement of C-peptide levels are suggested to be performed in a gynecological patient who underwent chemotherapy.

No assessment of all factors related to pancreatic Langerhans function in this study remained one of the limitations of this study, disabling a further understanding of the pathophysiology of the long and complex mechanism of C-peptide secretion in-vivo. In addition, this study did not directly determine the sensitivity of pancreatic Langerhans cells to carboplatin and assess the dynamic of glucose level changes in each cycle of chemotherapy due to the requirement of a larger sample size. A study with larger sample sizes was needed to understand this.

CONCLUSIONS AND SUGGESTIONS

It was concluded from this study that serum C-peptide levels were lower in the second group compared to the first group; therefore, serum C-peptide levels in gynecological patients who underwent chemotherapy with carboplatin were able to be used to assess disease progression in treatment complications as "other type of diabetes" . A cohort study with larger samples following C-peptide and glucose monitoring in every

cycle of chemotherapy was needed to observe the beginning of lowering the C-peptide level to enable early observation and treatment.

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