The Comparison of Neutropenia and Peripheral Neuropathy Condition as an Impact of 3-hours and 24-hour Paclitaxel Infusion of Paclitaxel-Carboplatin Chemotherapy on Ovarian Cancer Patients

Primandono Perbowo, Brahmana Askandar, Sunjoto, Ratna D Soebadi, Ahcmad Bashori

Gynaecologic Oncology Division, Dept. Obstetrics and Gynaecology Airlangga University, dr. Soetomo Surabaya Public Hospital, Indonesia

Abstract. *This study is aimed to compare the difference of neutropenia with peripheral neuropathy condition, after administration of 3 hours and 24 hours Paclitaxel infusion in adjuvant therapy with Paclitaxel-Carboplatin toward patient with ovarian carcinoma. The method that used was experimental research with samples randomized after consecutively recruited based on inclusive criteria. Before and every after chemotherapy, NCS was performed and differential count laboratories' test and then analysed with T-test and Chi-square test. The result showed that from three times administration of 3 hours Paclitaxel-Carboplatin infusion group, the neutropenia condition after first up to third chemotherapy was 20 %, 30 %, 30 %, and the peripheral neuropathy condition was 30 %, 60 %, 50 % respectively. Meanwhile, in 24 hours Paclitaxel-Carboplatin infusion group, the incident of neutropenia after first up to third chemotherapy was 40 %, 50 %, 40 %, and the incident of peripheral neuropathy was 20 %, 20 %, 20 % respectively. The statistic result was $p > 0.05$. Hence, there was no significant difference in neutropenia and peripheral neuropathy incident on two study group.*

Key words: *Neutropenia, Peripheral Neuropathy, Paclitaxel, Carboplatin, Ovarian Carcinoma, Neuro Conduction Study.*

Introduction

Among 15 types of cancers existing in the world, three of them are gynaecologic cancers including cervical cancer, ovarian cancer, and womb cancer. Ovarian cancer is also considered as the 4th mortality cause after lung, breast, and colon cancers [1, 2, 3].

The problem of ovarian cancer in developing countries is considered to be of high prevalence. Some cases which are discovered on the advanced stadium will cause the increase of morbidity and mortality of patients [4]. Hence, it is necessary to obtain optimal therapy toward cancers which are determined by its stadium, differentiation level, fertility, and general condition of the patients.

In this case, the neoadjuvant chemotherapy (performed before the surgery) aims to repress the growth of tumour and reduce the attachment with the surrounding

tissues, therefore it will ease the surgery techniques and if it is possible, surgical staging will be obtained. Patients who suffer from high risk groups' ovarian cancer (stadium 1 with differentiation degree 3, stadium 1C, stadium 2, and clear cell tumor) will be given chemotherapy [5, 3, 6].

The controversy in choosing chemotherapy regiment, time duration variations and the amount of dosage has not found the valid formula yet, in which it aims to get the effective results as well as minimum side effect, and thus will lead to improving of life quality [7, 8].

Paclitaxel is defined as medicine that has anti-cancer effect since 1960s. The combination *Paclitaxel-Carboplatin* is often used due to tolerated side effect than *Paclitaxel-Cisplatin*, although there is no difference in therapy response. The Paclitaxel original schedule that agreed by experts is along 24 hours. However, there are a lot of clinical experiences which report that 24-hour infusion has several weaknesses. The weaknesses significantly cause *myelosupression* side effect such as neutropenia, the patients' level of comfort is neglected due to the duration of infusion that will increase the risk of nosocomial infections without setting aside the amount of dosage and combination with the platinum-based drugs, as well as it takes much costs to stay in hospital. This condition made some experts provide variation infusion start from 1 hour, 3 hours, 6 hours, 24 hours, and 96 hours in each educational and research development [9, 10, 11, 12].

It is mentioned in literature and studies that the differentiations of dosage are 135 mg/m^2 for 24-hour infusion and 175 mg/m^2 for 3-hour infusion – an internationally agreed standard (FIGO). Among the groups of 3 hours and 24 hours, it is known that there are no significant differentiation in progression-free survival, disease-free survival, and survival rate.

Some studies which evaluated side effects of 3-hour and 24-hour infusion obtained different results. The side effects were hypersensitivity, nausea and vomiting, nephrotoxicity, hepatotoxicity, peripheral neuropathy and neutropenia. Some studies have stated differently regarding on the phenomenon of high and low side effect; some of them stated no significant differences yet. Therefore, further research is required to identify the side effects of *Paclitaxel-Carboplatin* infusion including dosage, interval and duration that aimed to enhance knowledge about absorption, distribution, metabolism, elimination, medicine response's profile and its effectiveness [13, 14, 15, 16].

Heretofore, there was no study evaluating side effects of duration differentiation in chemotherapy infusion in Indonesia. Since, the research is obtained in the dr. Soetomo Public Hospital where 5–6 patients among huge amount of patients can endure chemotherapy a day. For the consideration of time efficiency, this study conducted 3-hour Paclitaxel infusion. Thus, a researcher would like to compare 3-hour and 24-hour *Paclitaxel-Carboplatin* infusion in relation with neutropenia and peripheral neuropathy condition in Indonesian society.

Method

Research Design

This study was an experimental research illustrated by graphics below:
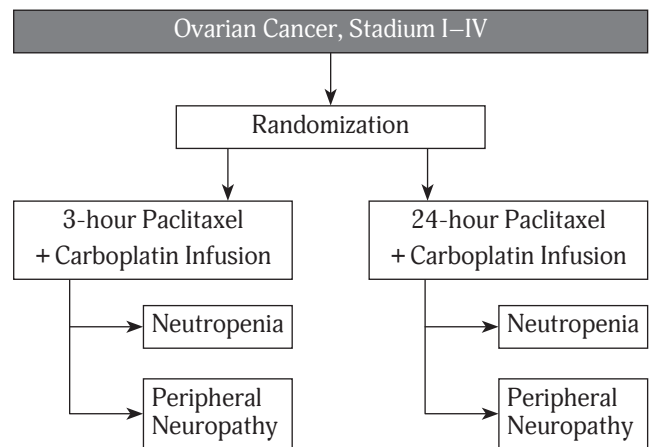
This study was conducted in Obstetrician Research Centre, Medical Rehabilitation Department, and Pathology clinic of dr. Soetomo Public Hospital of Surabaya. The population of this study was stadium I–IV ovarian cancer patients. Some of the samples had inclusion and exclusion characteristics. Moreover, in sampling technique, consecutive sampling was used. Samples were randomised by double blind to divide them into 3-hour and 24-hour *Paclitaxel-Carboplatin* infusions.

The sample amount used in this study was based on the following formula:

$$n1 = n2 = \frac{(Z\,1/2\alpha + Z\,\beta)^2\,p \times q}{(p1 - p2)^2}$$

Significance level → α = 0,05 → Z 1/2 α = 1,96
Test power (1 − β) → β = 0,20 → Z β = 0,842

n1 = sample group of 3-hour infusion
n2 = sample group of 24-hour infusion
z = default value in normal distribution

$$q = 1 - p = 1 - 0{,}373 = 0{,}627$$

p = neutropenia chemotherapy in *Paclitaxel-Carboplatin* proportion

$$n1 = n2 = \frac{(1.96 + 0.84)^2 \times 0.373 \times 0.627}{(0.315)^2} = 9.8 \sim 10$$
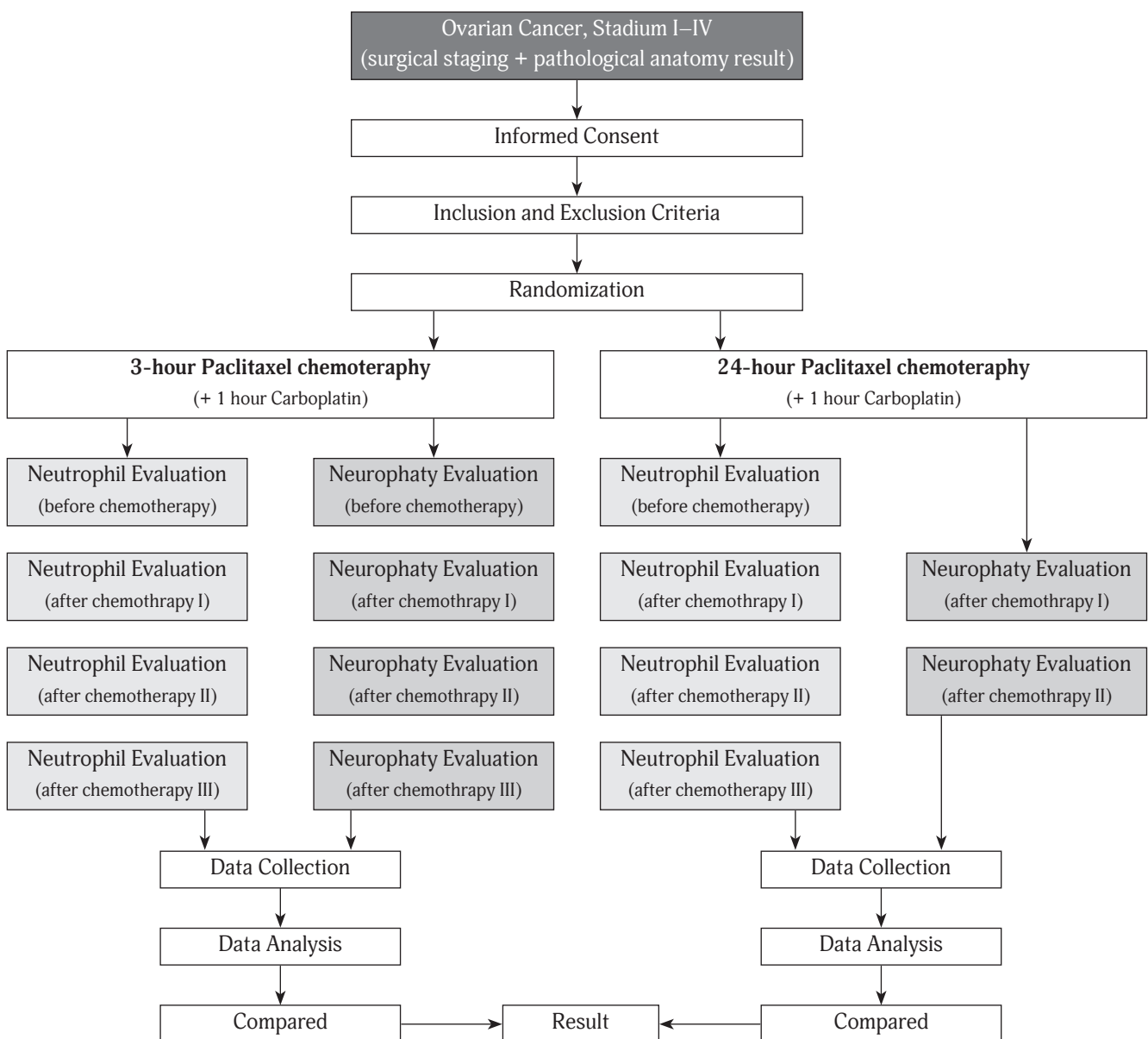
n1 = n2 = 10 samples

The minimum sample in this study was 10 patients in each group and the total amount – 20 samples.

Sample Criteria

1. Inclusion Criteria
   - Patients with ovarian cancer, stadium I–IV (based on FIGO) whether endured optimal or suboptimal surgical debulking of tumours.
   - Fulfilled chemotherapy requirements:

- Haematology normal ranges: Hb > 10 g %, leukocytes > 3.0×10^3 /μL or < 12.0×10^3 / μL, platelet > 100 000.
- Kidney and liver normal functioning.
- Consent to participate in this study by signing *informed consent*.
2. Exclusion Criteria:
   - Previous chemotherapy.
   - Suffering from other peripheral neuropathy disease (diabetes mellitus).
3. Drop Out Criteria:
   - Patient death.
   - Not regular treatment.

Ovarian Cancer, Stadium I–IV
(surgical staging + pathological anatomy result)

↓

Informed Consent

↓

Inclusion and Exclusion Criteria

↓

Randomization

┌──────────────────────────┴──────────────────────────┐

3-hour Paclitaxel chemoteraphy
(+ 1 hour Carboplatin)

24-hour Paclitaxel chemoteraphy
(+ 1 hour Carboplatin)

Neutrophil Evaluation (before chemotherapy) | Neurophaty Evaluation (before chemotherapy) | Neutrophil Evaluation (before chemotherapy)

Neutrophil Evaluation (after chemothrapy I) | Neurophaty Evaluation (after chemothrapy I) | Neutrophil Evaluation (after chemothrapy I) | Neurophaty Evaluation (after chemothrapy I)

Neutrophil Evaluation (after chemotherapy II) | Neurophaty Evaluation (after chemothrapy II) | Neutrophil Evaluation (after chemotherapy II) | Neurophaty Evaluation (after chemothrapy II)

Neutrophil Evaluation (after chemotherapy III) | Neurophaty Evaluation (after chemothrapy III) | Neutrophil Evaluation (after chemotherapy III)

Data Collection | Data Collection

↓ | ↓

Data Analysis | Data Analysis

↓ | ↓

Compared → Result ← Compared

Research Flowchart

Results

The research was conducted from December 2008 up to May 2009 in the dr. Soetomo Public Hospital, Surabaya. Along the period of research, 20 samples were included into the study. It also involved 10 groups of patients of 3-hour Paclitaxel infusion and 10 groups of patients of 24-hour Paclitaxel infusion.

Each of research subject was checked for peripheral neuropathy in the Medical Rehabilitation Laboratory as well as for neutropenia in the Clinical Pathology Laboratory before the chemotherapy was obtained and after the first, second, and third chemotherapy.

This study used significant level 0.05 (5 %), so that if the ballistic testing were $p \leq 0.05$ then it can be signifi-cant. Meanwhile, if the ballistic testing were $p \geq 0.05$, it was not significant.

Sample Characteristics

Table 1 showed that the average age of 3-hour infusion group (47.2 + 5.61) was the same as for 24-hour infusion group (47.3 + 5.88). The result is proved by 2 free samples of T-test which were found to be $p > 0.05$, so it means that statistically, there was no significant difference in the mean age of patients.

The average of body area of 3-hour infusion group (1.50 $\pm$ 0.12) was the same as 24-hour infusion group (1.52 $\pm$ 0.10). The result is proved by 2 free samples of T-test which were found to be $p > 0.05$, so it means that statistically, there was no significant difference in the mean body area.

Table 1. Patients' general characteristics

Characteristics	3-hour Infusion		24-hours Infusion		Statistical Testing
Age (Years)	Frequency	%	Frequency	%	
30–40	0	0 %	0	0 %	T-test
41–50	8	80 %	6	60 %	
51–60	2	20 %	4	40 %	Pricing ratio p = 0.96
Total Amount	10	100 %	10	100 %	
Body Area					
1.30–1.40	2	20 %	1	10 %	T-test
1.41–1.50	3	30 %	2	20 %	
1.51–1.60	3	30 %	6	60 %	Pricing ratio p = 0.75
>1.61	2	20 %	1	10 %	
Total Amount	10	100 %	10	100 %	
Hb					T-test
10.0–10.9	2	20 %	2	20 %	
11.0–11.9	2	20 %	2	20 %	Pricing ratio p = 0.76
12.0–12.9	3	30 %	3	30 %	
≥ 13.0	3	30 %	3	30 %	
Total Amount	10	100 %	10	100 %	
Albumin					
2.75–3.49	4	40 %	4	40 %	T-test
3.50–3.99	4	40 %	5	50 %	
≥ 4.00	2	20 %	1	10 %	Pricing ratio p = 0.68
Total Amount	10	100 %	10	100 %	

Furthermore, the average haemoglobin for 3-hour infusion group (11.9 ± 1.1) was the same as 24-hour infusion group (12.1 ± 1.2). The result isproved by 2 free samples which were found to be p > 0.05, so it means that there was no significant difference of haemoglobin.

Then, the average of albumin for 3-hour infusion group (3.5 ± 0.4) was the same as for 24-hour infusion group (3.6 ± 0.3). The result of T-test free samples was obtained – pricing ration p > 0.05, so it means that statistically, there were no significant difference of average albumin.

From the Table 2, it was obtained that in ovarian cancer stadium 3-hours infusion group there were IC (50 %) and IIIC (50 %). Meanwhile, in the 24-hour infusion group there were IC (60 %) and IIIC (40 %). Then, the result of Chi-square is obtained – pricing ratio p = 1.00 (> 0.05), so it means that there was no significant difference in clinical ovarian cancer.

The effort to get the right sample between the two groups was optimally obtained through statistical analysis. From 20 samples, it was seen that the two groups statistically showed no significant difference in age, body area, haemoglobin, albumin, as well as cancer clinical stadium. Hence, it could be said that the sample was homogeneous.

Result Analysis

Chi-square test

From Table 3, it was obtained that neutropenia condition in the 3-hour infusion group after chemotherapy was Paclitaxel-Carboplatin I (20 %), Paclitaxel-Carboplatin II (30 %), and Paclitaxel-Carboplatin III (30 %). Meanwhile, in the 24-hour infusion group, the result of Chi-square test obtained that the pricing ration p > 0 05, thus there was no significant difference in neutropenia condition of chemotherapy I, II, and III between 3-hour and 24-hour infusion.

Figure 1 figure showed the average amount of neutrophils which begin to decrease from chemotherapy I up to chemotherapy III. The decreasing is much bigger in the 24-hour infusion group rather than in the 3-hour group. The result of T-test showed that in the 24-hour

Table 2. The characteristics of patients' stadium of ovarian cancer

Stadium	3-hour infusion		24-hour infusion			
	Frequency	%	Frequency	%	Total	%
I c	5	50 %	6	60 %	11	55 %
III c	5	50 %	4	40 %	9	45 %
Total Amount	10	100 %	10	100 %	20	100 %

Table 3. Neutropenia condition after chemotherapy

Paclitaxel-Carboplatin I	3-hour infusion		24-hour infusion				Pricing ratio p
	Frequency	%	Frequency	%	Total	%	
Neutropenia (+)	2	20 %	4	40 %	6	30 %	p = 0.62
Neutropenia (-)	8	80 %	6	60 %	14	70 %	
Total	10	100 %	10	100 %	20	100 %	
Paclitaxel-Carboplatin II							
Neutropenia (+)	3	30 %	5	50 %	8	40 %	p = 0.65
Neutropenia (-)	7	70 %	5	50 %	12	60 %	
Total	10	100 %	10	100 %	20	100 %	
Paclitaxel-Carboplatin III							
Neutropenia (+)	3	30 %	4	40 %	7	35 %	p = 1.00
Neutropenia (-)	7	70 %	6	60 %	13	65 %	
Total	10	100 %	10	100 %	20	100 %	

Average Amount of Neutrophils(cell/mm^3)

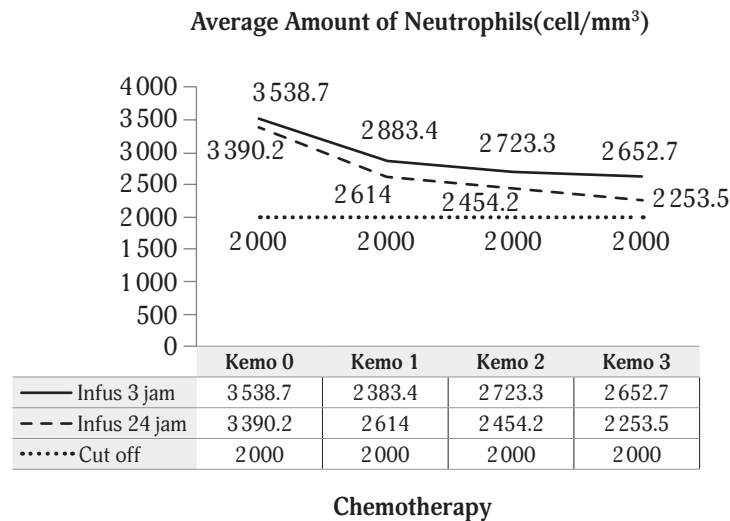|	Kemo 0	Kemo 1	Kemo 2	Kemo 3
—— Infus 3 jam	3 538.7	2 383.4	2 723.3	2 652.7
– – – Infus 24 jam	3 390.2	2 614	2 454.2	2 253.5
······ Cut off	2 000	2 000	2 000	2 000

Chemotherapy

Fig. 1. The differences of decreasing amount of neutrophils

infusion, the decrease of neutrophils before and after chemotherapy I obtained significant result (p < 0.0001), after chemotherapy II it also obtained significant result (p = 0.03), however, after chemotherapy III the result was insignificant (p = 0.11).

Meanwhile, in the 3-hour infusion group T-test result showed a decrease in neutrophils before and after chemotherapy I – significant result (p < 0.0001). But after chemotherapy II, there were no significant results (p = 0.281), and after chemotherapy III also there were no significant results (p = 0.252).

T-test

In the Table 4, concerning 3-hour infusion, it was obtained that before chemotherapy and after chemotherapy I, the amount of neutrophil was decreasing up to 19 %. After chemotherapy II, the result compared to chemotherapy I showed decreasing up to 5.9 % and after chemotherapy III – decreasing up to 1.2 %. On the other hand, in the 24-hour infusion group, before and after chemotherapy I the amount of neutrophils decreased to 23.8 %, after chemotherapy II – 7.5 %, and after chemotherapy III – 8.6 %. In the T-test, the comparison between the amounts of neutrophils in the 3-hour infusion group and 24-hour infusion group, there was no significant difference with the amount p > 0.05 whether after chemotherapy I, II, or III.

Chi-square test

Table 5 shows neuropathy condition in the 3-hour infusion group after chemotherapy Paclitaxel-Carboplatin I (30 %), Paclitaxel-Carboplatin II (60 %), and Paclitaxel-Carboplatin III (50 %). Meanwhile, in the 24-hour-infusion group, neuropathy condition after Paclitaxel-Carboplatin I was 20 %, after Paclitaxel-Carboplatin II – 20 %, and after Paclitaxel-Carboplatin III – 20 %. Then, the result of Chi-square test obtained pricing ratio p > 0.05, so there was no significant neuropathy condition in the chemotherapy I, II, and III in the 3-hour and 24-hour infusion group.

Figure 2 showed that the average amplitude wave is continuously decreasing. The decreasing in the 3-hour infusion group is more significant than in the 24-hour infusion group. The T-test showed that the decreasing of amplitude wave was significantly clear after and before chemotherapy I (p = 0.009), as well as after chemotherapy III and II (p = 0.007). While, in the 24-hour infusion group, the decreasing of amplitude wave was clearly significant after and before chemotherapy I (p < 0.0001), after chemotherapy II and chemotherapy I (p = 0.04), and after chemotherapy III and chemotherapy II (p = 0.15).

T-test

Table 6 shows the decreasing of amplitude wave about 16.8 % in the 3-hour infusion group after and before

Table 4. Percentage of decreasing amount of neutrophils in each chemotherapy

	Chemotherapy I–0	Chemotherapy II–I	Chemotherapy III–II
3 hours	19.0 %	5.9 %	1.2 %
24 hours	23.8 %	7.5 %	8.6 %
Pricing ratio p	0.37	0.77	0.24

Table 5. Neuropathy condition after chemotherapy

Paclitaxel-Carboplatin I	3-hour infusion		24-hour infusion				Pricing ratio p
	Frequency	%	Frequency	%	Total	%	
Neuropathy (+)	3	30 %	2	20 %	5	25 %	
Neuropathy (-)	7	70 %	8	80 %	15	75 %	p = 1.00
Total	10	100 %	10	100 %	20	100 %	
Paclitaxel-Carboplatin II							
Neuropathy (+)	6	60 %	2	20 %	8	40 %	
Neuropathy (-)	4	40 %	8	80 %	12	60 %	p = 0.17
Total	10	100 %	10	100 %	20	100 %	
Paclitaxel-Carboplatin III							
Neuropathy (+)	5	50 %	2	20 %	6	30 %	
Neuropathy (-)	5	50 %	8	80 %	14	70 %	P = 0.35
Total	10	100 %	10	100 %	20	100 %	

Average Amplitude NCS (mV)

	NCS 0	NCS 1	NCS 2	NCS 3
—— Infus 3 jam	4.14	3.45	2.38	2.04
– – Infus 24 jam	3.6	2.84	2.51	2.28
····· Cut off	2	2	2	2
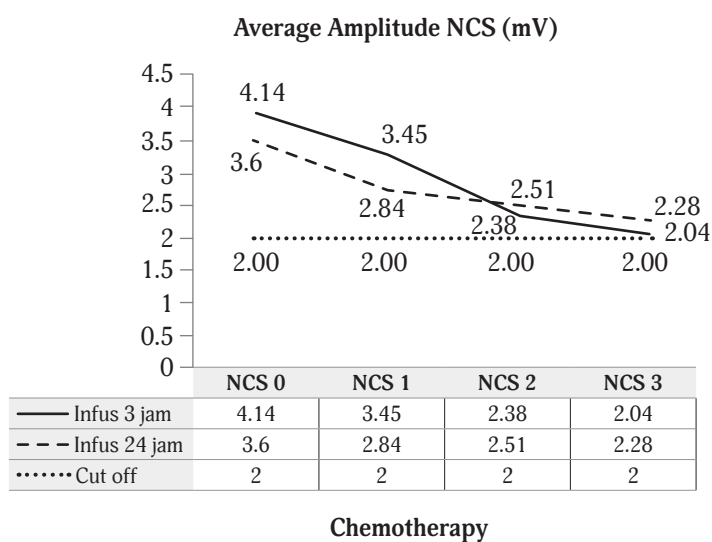
Chemotherapy

Fig. 2. Difference of decreasing amplitude wave

Table 6. Percentage of the decreasing of amplitude wave after chemotherapy

	Chemo-therapy I–0	Chemo-therapy II–I	Chemo-therapy III–II
3 hours	16.8 %	29.1 %	21.0 %
24 hours	20.8 %	12.3 %	9.3 %
Pricing ratio p	0.64	0.11	0.17

chemotherapy I, after chemotherapy II – 29.1 % if compared to chemotherapy I, and after chemotherapy III – 21.0 %. In the 24-hour infusion group, before and after chemotherapy I, the decreasing amount of neutrophils was about 20.8 %, after chemotherapy II – 12.3 % if compared to chemotherapy I, and after chemotherapy III– 9.3 %. The T-test showed no significant difference in p > 0.05 whether after chemotherapy I, II, or III.

Discussion

The combination of *taxane* wave (Paclitaxel-Docetaxel) with the platinum-based wave (Cisplatin-Carboplatin) is a kind of chemotherapy regiment for ovarian cancer in which there are hot issues to discuss and research to obtain since it become the primary choose in the chemotherapy medicine.

Hence, this study is obtained to scrutinize the difference between side effects – neutropenia and neuropathy after chemotherapy Paclitaxel-Carboplatin given in 3 and 24 hours of infusion to ovarian cancer patients, in which the surgical staging was optimally performed since December 2008 up to May 2009.

The side effect that most often occurs in Paclitaxel-Carboplatin is hypersensitive reaction. Grant and Kris reported in the study the phase I – there was obtained a hypersensitive reaction about 30–40 % during 3-hour infusion. The risk will be increasing if Paclitaxel-Carboplatin is given in short time. In the implementation, the pre-medication with the help of corticosteroid was helping to reduce this kind of reaction, thus, in the further study, on phase II, phase III, and phase IV, hypersensitive condition will rarely happen [17].

In this study, researchers have found that 2 patients from 3-hour infusion group and 1 patient from 24-hour infusion group were experiencing hypersensitiveness. The symptoms can be in the form of urticarial itch but not shock. However, the implementation of infusion should be rapid and precise so that patients will not get into shock condition. It can be performed by controlling airways, breathing, and circulation which include evaluation of airways, giving oxygen mask, and live saving infusion.

Sample characteristics

Total of samples involved into this study were 20 patients with ovarian cancer and obtained optimum surgical staging and adjuvant Paclitaxel-Carboplatin chemotherapy. The average age of patients in the 3-hour infusion group – 47.2 $\pm$ 5.61, the average age of patients in the 24-hour infusion group – 47.3 $\pm$ 5.88. This result was proved by the T-test of 2 free samples which obtained pricing ratio p > 0.05. It means that statistically, there were no significant differences in patients' age. Furthermore, the average of body area in 3-hour infusion group was the same (1.50 $\pm$ 0.12) compared to 24-hour infusion group (1.52 $\pm$ 0.10). The T-test of free samples obtained the pricing ratio p > 0.05. It means that statistically, there were no significant differences in body area. The result of Chi-square test of ovarian cancer stadium on both of groups found that the pricing ratio p = 1.00 (> 0.05), so it means there were no significant differences.

Basic Variable Election

Researchers observed patients with ovarian cancer in dr. Soetomo Public Health Hospital, where they performed chemotherapy and suddenly become deteriorate, feeling unwell and weak, thus leading to sepsis condition. Afterward, the further observation was done and thus it was concluded that patients were getting neutropenia febrile – the condition that can cause death. Hence, researchers assumed that neutrophil was the first defence mechanism to the infection where neutrophil was the biggest part of leukocyte – about 50–60 %. Neutropenia then considered as the most frequent side effect in chemotherapy using Paclitaxel and Carboplatin.

The side effect of non-haematology which caused pain from cancer metastases was peripheral neuropathy. From several literatures, it was mentioned that medical treatment by neutrophil groups did not provide therapy improvement and the effect of neutrophil will lead to the progress of cancer (resistant). Nowadays, the degree of peripheral neuropathy based on WHO and ECOG merely depends on the subjective lamentation, yet no agreement toward objective treatment as gold treatment standard. From the previous studies, NCS (Nerve Condition Study) was an objective observation tool often used due to its sensitivity and good specification to know the first symptom from peripheral neuropathy condition.

Result Analysis

In the general characteristics of 20 samples, both of the groups did not show signs and symptoms of neutropenia and peripheral neuropathy before the chemotherapy. Statistically, there were no significant differences in age, body area, and clinical stadium of patients while given Paclitaxel-Carboplatin in the 3- and 24-hour infusion groups. Meanwhile, Kolmogorov-Smirnov Z test found the value p > 0.05 which means that all of the samples were homogeneous, and did not affect the further comparison.

Comparison of Neutropenia between the two Groups in Paclitaxel-Carboplatin Chemotherapy

Neutropenia is described as side effect of chemotherapy that by age, balance or imbalance nutrition, kidney and liver disease, experience of chemotherapy/radiation in previous, infection factors, post-surgery/wounds opens by the invasion of cancer cell. The degree of neutropenia depended on the result of absolute neutrophil count (ANC) under 2 000 cell/mm³. ANC then depicted as the amount of leucocytes and polimorphonuclear cell fraction (PMN) and band form according to the pattern below:

$$\text{ANC} = \text{leucocyte cell (cell/mm}^3) \times \text{percentage (PMNs} + \text{bands)} : 100$$

In this study, it was found that neutropenia in 24-hour infusion group was 50 %, while in the 3-hour group infusion – 30 %. From the 24-hour infusion group, there were 2 patients of neutropenia degree 1, 2 patients of neutropenia degree 2 with the amount of leucocytes $< 4,0 \times 10^3/\mu L$ and the amount of neutrophils – no more than 1 500 cell/mm^3, also a patient degree 3 in which the amount of leucocytes was $< 4,0 \times 10^3/\mu L$ and the amount of neutrophils – less than 1 000 that necessary to get G-CSF injection therapy. Afterward, in the 3-hour infusion group, it was obtained that 3 patients of neutropenia degree 1 did not need to get G-CSF therapy. Thus, there was no significant difference after chemotherapy I, II, and III from both of the groups with statistical value p > 0.05.

The decrease of the amount of neutrophils was higher in the 24-hour infusion group than in the 3-hour infusion group. The T-test in the 24-hour infusion group showed that the decreasing of neutrophils before and after chemotherapy I obtained the significant result (p < 0.0001), after chemotherapy II and I it also obtained the significant result (p = 0.03), however after chemotherapy III, the result was insignificant (p = 0.11). In the 3-hour infusion group, the decreasing of the amount of neutrophils before and after chemotherapy I obtained the significant result (p < 0.0001), but unfortunately, after chemotherapy II the result was insignificant (p = 0.281), and after chemotherapy III, the result remained insignificant (p = 0.252). Thus, it strengthens the theory which mentioned that the highest decrease of the amount of neutrophils was after the implementation of chemotherapy I, since there was an organ and tissues cell shock condition, thus it would lead to adaptation by increasing the production of progenitor cell/stem cell after several chemotherapies.

The neutropenia condition of 3-hour infusion group happened for patients of old age and in the state of high stadium (IIIC). Meanwhile, in the 24-hour infusion group, the difference incidence was obtained, in which the neutropenia condition occured in the former stadium. Therefore, it can be concluded that neutropenia condition in the 3-hour infusion group was not merely influence by the time dependent factor and dosage, but it also depends on other extrinsic factors such as interval between further chemotherapy, haemoglobin, lipid/albumin profile. Furthermore, it also assumed that it was influenced by intrinsic factors such as progression of cancer cell of further stadium to the bone marrow which can affect bonding/communication between cells compared to the 24-hour group infusion [18, 19, 20].

The results of this study were the same as Kris' (1995) for breast cancer (paclitaxel dosage 190 mg/m^2), Schiller' and Sarosy' for ovarian cancer further stadium (Paclitaxel

dosage 210 mg/m^2 dan 250 mg/m^2 + G-CFS) stated that in the 24-hour infusion group, there was no significant difference in neutropenia compared to the 3-hour infusion group.

Meanwhile, the difference showed by Rowinsky and Donehower in which the amount of neutropenia condition was bigger in the group 1 – 6 hours. Ohtsu (1995) added that the dosage for 3 hours was 210 mg/m^2 and for 24 hours – 135 mg/m^2, then the amount of neutropenia in the 3-hour infusion group was less than those for 24-hour infusion group (40.7 % versus 66.7 %). Wiernik et al. stated that the dosage should be paclitaxel 250 mg/m^2, and Ohnuma added that the dosage 200 mg/m^2 would increase the side effect of neutropenia, since the neutropenia was dosage dependent, time dependent, and Paclitaxel-carboplatin infusion. Jennens used each of dosage 175 mg/m^2 and obtained that there was no significant difference between 3- and 6-hour infusions, but it obtained an increase in the neutropenia in the 24-hour infusion group. Peretz stated that significant difference between neutropenia in the 3- and 24-hour infusion groups were 30 % and 60 % using paclitaxel 175 mg/m^2 (n = 521) [13, 14, 18, 19, 20, 21].

Table 3 showed that neutropenia condition mostly occurs after the first treatment with Paclitaxel-Carboplatin and it starts to stabilize in the second and third chemo-therapy. It caused by the adaptation in the stem cell. There was no significant difference between the 3- and 24-hour infusion groups after chemotherapy I (20 % ver-sus 40 %). Furthermore, acute granulocytopenia occurs 6–12 days after the chemotherapy, and the recovery oc-curs in 10–14 days. Thus, it can be used as consideration that the right time to obtain further chemotherapy $\pm$ 21 days. Besides the amount of dosage given, the duration of chemotherapy infusion and clinical stadium, other factors which influence neutropenia condition is the age factor and malnutrition.

Figure 5 and Table 4 showed that administration of Paclitaxel-Carboplatin during 24-hour infusion can cause decrease of the amount of neutrophils higher than those during 3-hour infusion. Theoretically, this was caused by the duration of chemotherapy medicine concentration in the plasma in steady state which is above the physiological threshold value (Vss↑ and MRT↑) giving longer time for blood flow to carry active drug substances from the central compartment to the tissues' compartment. Then it penetrates into the body's tissue, especially the bone marrow and influencing the stages of hematopoietic/hemocytoblast cell division and maturation due to the mitotic spindle transport that will lead to maturation defect and the reduced amount of neutrophils [8, 13, 14].

Comparison of Peripheral Neuropathy between the two Groups in Paclitaxel-Carboplatin Chemotherapy

In this study, the side effects of peripheral neuropathy in the 24-hour infusion group were 30 %. Meanwhile, in the 3-hour infusion group – 60 % with the statistical test p > 0.05. Therefore it can be concluded that there were no significant difference. In the table 5, a clear difference was obtained in which the peripheral neuropathy in the 3-hour infusion group occurred after the administration of Paclitaxel-Carboplatin II (60 %). Meanwhile in the 24-hour infusion group, there was no difference either after the first, second, or even third chemotherapy (20 %).

In the 3-hour infusion group, the tendency of neuropathy to be apparent after the second chemotherapy in which it obtained the significant result (p = 0.031), while in the 24-hour infusion group, the tendency of neuropathy was not significantly different before and after first chemotherapy (p = 0.500), second chemotherapy (p = 0.500), and third chemotherapy (p = 0.500). However, it was strengthen by the NCS observation which was apparent in the decreasing of amplitude wave in the 3-hour infusion group compared to 24-hour infusion group. The T-test showed the decrease in amplitude wave in the 3-hour infusion group significant either after the first chemotherapy and before the second chemotherapy (p = 0.05), after second chemotherapy with the first chemotherapy (p = 0.009), and after the third chemotherapy with the second chemotherapy (p = 0.007). Meanwhile, in the 24-hour infusion group, the decrease of amplitude wave was significantly clear after the first chemotherapy before second chemotherapy (p < 0.0001), after second chemotherapy with the first chemotherapy (p = 0.04), it does not occur after the third chemotherapy with the second chemotherapy (p = 0.15).

In this study, researchers found that a patient from 3-hour infusion group had neuropathy degree increasing, either from subjective lamentation or NCS observation (degree 2–3) after the second series chemotherapy, hence, researchers tried to reduce paclitaxel dosage which was about 20 %. A patient from 3-hour infusion group after the first chemotherapy had tingling lamentation and the NCS result showed that there was neuropathy in *n. suralis*, but after further chemotherapy the condition was reversible. Then, it concluded that the patient had light neuropathy lamentation in which *n. suralis* just merely hadfunction as sensory. Most of patients from 3-hour infusion group or 24-hour infusion group from the NCS observation had peripheral neuropathy in *n. peroneus* compared with *n. tibialis*. In this case, it was possible since the *n. peroneus* diameter was tinier than *n. tibialis*, so that the amount of nerve fibres was also less and if the number of nerve fibres were the same between *n. tibialis* and *n. peroneus*. Hence, *n. peroneus* was not reversible [22].

This result was similar with the research obtained by Smith in National Surgical Adjuvant Breast and Bowel Project B-26 toward breast cancer patients, peripheral neuropathy grade 3–4 which occured in 22 % of patients and included into 3-hour Paclitaxel infusion group (250 mg/m^2; n = 279) and 13 % of patients included into 24-hour Paclitaxel infusion group (250 mg/m^2; n = 284). In a paclitaxel randomization phase III (135 or 175 mg/m^2) in ovarian carcinoma, there was no significant difference in the peripheral neuropathy condition grade 3–4 which is about 0.7 % in the 3-hour infusion group (n = 187) and 0.6 % in 24-hour infusion group (n = 204). Peretz stated that patients with breast cancer had compared paclitaxel 175 mg/m^2 (n = 521) between 3- and 24-hour infusion groups found that peripheral neuropathy was 78 % versus 65 % (insignificant) [21].

According to Rowinsky and Donehower, the side effect of peripheral neuropathy was tending to the usage of dosage. They proved that in recurrent ovarian cancer patients with paclitaxel dosage between 135 mg/m^2 up to 250 mg/m^2 in the 3-hour infusion group if compared to 24-hour infusion group, there were no significant difference. But, with the dosage > 250 mg/m^2, then peripheral neuropathy will appear and not be influenced by the infusion duration [18].

However, the difference result showed by Ohtsu (1995) with the 3-hour dosage infusion is about 210 mg/m^2; n = 27 and the 24-hour infusion were 135 mg/m^2; n = 15. The number of peripheral neuropathies in the 3-hour infusion group was bigger than for 24-hour infusion group (63 % versus 6.4 %) [13].

According to McPhee, the factors that influence the emergence of side effects in peripheral neuropathy were the magnitude of dosage, age, nutritional status, diabetes mellitus, long-term consumption of alcohol and the interval time between chemotherapy and surgical staging surgery [22].

In Figure 2 and Table 6, the administration of 3-hour Paclitaxel-Carboplatin infusion tends to have greater peripheral neuropathy as evidenced by a decrease in the amplitude wave *n. peroneus* compared to 24-hour infusion. Theoretically, the incidence of peripheral neuropathy has increased during 3-hour infusion due to the presumption that maximal concentration (C_{max}) was achieved in a short time (t_{max}) accompanied by higher dosages as the main determinant. However, it was found only in the central compartment but not in the tissue compartment causing distribution (MRT), and elimination would become saturated in proportion to the length of exposure, and drug dosage would inhibit body neuron cells and Schwann cells that have excellent blood vessel cyclic velocity and the cell cycle is rapid, G_2/M phase lasts 3–4 hours thus caus-

ing inhibition of cell proliferation and regeneration does not work well [11].

Conclusion

Based on the result of the research, it can be concluded that there was no significant increase in neutropenia in the 24-hour Paclitaxel infusion group compared to the 3-hour infusion group in Paclitaxel-Carboplatin adjuvant therapy. Afterward, it did not obtain the significant increase toward peripheral neuropathy in the 3-hour Paclitaxel infusion group compared to 24-hour infusion group in adjuvant Paclitaxel-Carboplatin therapy.

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Порівняння нейтропенії та периферичної нейропатії після 3-годинної та 24-годинної інфузії Паклітакселу в складі хіміотерапії Паклітаксел-Карбоплатином у пацієнтіок із раком яєчників

Primandono Perbowo, Brahmana Askandar, Sunjoto, Ratna D Soebadi, Ahcmad Bashori

Відділ гінекологічної онкології, відділення акушерства та гінекології Університету Айрлангга, Державна лікарня імені Соетомо, м. Сурабая, Індонезія

Резюме. *Метою дослідження було порівняти різницю у нейтропенії та стані периферичної нейропатії після призначення 3-годинної та 24-годинної інфузії Паклітакселу в складі ад'ювантної хіміотерапії Паклітаксела-Карбоплатином у пацієнтів із карциномою яєчників. Були використані методи експериментального дослідження із включенням пацієнтів після перевірки критеріїв включення. Рівні нейтрофілів та диференційна лабораторна панель перевірялись до і після кожної хіміотерапії з наступною статистичною оцінкою Т-критерію та критерію Пірсона. Результати показали, що після триразового 3-годинного введення Паклітакселу-Карбоплатину стан нейтропенії від першого до третього введення спостерігався у 20 %; 30 %; 30 % і периферичної нейропатії — у 30 %; 60 %; 50 % відповідно. У той же час при 24-годинній інфузії частота нейтропенії складала 40 %; 50 %; 40 % і частота периферичної нейропатії — 20 %; 20 %; 20 % відповідно. Статистична достовірність склала р > 0,05. Не було виявлено значної різниці у частоті нейтропенії та периферичної нейропатії у двох досліджуваних групах.*

Ключові слова: *нейтропенія, периферична нейропатія, Паклітаксел, Карбоплатин, карцинома яєчників, дослідження нервового проведення.*

Сравнение нейтропении и периферической нейропатии вследствие 3-часовой и 24-часовой инфузии Паклитаксела в составе Паклитаксел-Карбоплатиновой химиотерапии у пациенток с раком яичников

Primandono Perbowo, Brahmana Askandar, Sunjoto, Ratna D Soebadi, Ahcmad Bashori

Отдел гинекологической онкологии, отделение акушерства и гинекологии Университета Айрлангга, Государственная больница имени Соетомо., г. Сурабая, Индонезия

Резюме. *Целью исследования было сравнить разницу в нейтропении с состоянием периферической нейропатии после назначения 3-часовой и 24-часовой инфузии Паклитаксела в составе адъювантной химиотерапии Паклитаксела-Карбоплатина у пациентов с карциномой яичников. Были использованы методы экспериментального исследования с включением пациентов после проверки критериев включения. До и после каждой химиотерапии определялись уровни нейтрофилов и дифференциальная лабораторная панель с последующей статистической оценкой Т-критерия и критерия Пирсона. Результаты показали, что после трехкратного 3-часового введения Паклитаксела-Карбоплатина состояние нейтропении от первого к третьему введению составляло 20 %; 30 %; 30 % и периферической нейропатии — 30 %; 60 %; 50 % соответственно. В то же время при 24-часовой инфузии частота нейтропении составляла 40 %; 50 %; 40 % и частота периферической нейропатии — 20 %; 20 %; 20 % соответственно. Статистическая достоверность составила р > 0,05. Не было обнаружено значительной разницы в частоте нейтропении и периферической нейропатии в двух иследовательских группах.*

Ключевые слова: *нейтропения, периферическая нейропатия, Паклитаксел, Карбоплатин, карцинома яичников, исследования нервного проведения.*