

COMPARISON OF THREE CHEMOTHERAPY REGIMENS TO THE DECREASE IN LEUKOCYTES AND THE INCIDENCE RATE OF NEUTROPENIA IN PATIENTS WITH NASOPHARYNGEAL CANCER AT DR. HASAN SADIKIN GENERAL HOSPITAL BANDUNG

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Received: 25 September 2017, Revised and Accepted: 4 October 2017

ABSTRACT

Objective: Nasopharyngeal cancer is the ninth most common cancer in Indonesia. The death of cancer patients is not only caused by cancer itself, but also several other factors such as the side effects of chemotherapy. Some side effects that occurred are decrease in leukocytes and incidence of neutropenia. Neutropenia is the highest hematological toxicity caused by chemotherapy treatment which has final manifestation is death from systemic infection. The purpose of this study is to compare three chemotherapy regimens in causing a decrease in leukocytes and the incidence of neutropenia in the patients with nasopharyngeal cancer in RSUP. Dr. Hasan Sadikin Bandung.

Methods: The three chemotherapy regimens compared in this study are cisplatin, cisplatin/5-fluorouracil (5-FU), and carboplatin/paclitaxel. This research is an analytic observational study with retrospective data collection and cross-sectional analytic design. The data were obtained from the medical records of inpatients with nasopharyngeal cancer during January-December 2015; total data 86 nasopharyngeal carcinoma patient[s] (>18 years old, female and male) data had been analyzed in this study.

Results: The percentage of neutropenia incidence in cisplatin regimen is 8.3%, in cisplatin/5-FU is 14.3%, and in carboplatin/ paclitaxel is 18.6%.

Conclusion: The results showed that there are no significant differences ($p > 0.05$) in the three regimens in causing the reduction of leukocyte ($p = 0.327$) and the average of absolute neutrophil count ($p = 0.240$).

Keywords: Nasopharyngeal cancer, Leukocyte, Neutropenia, Cisplatin, Cisplatin/5-fluorouracil, Carboplatin/paclitaxel.

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INTRODUCTION

Cancer is one of the non-infectious diseases, also known as a non-communicable disease, which is a leading cause of mortality and morbidity worldwide [1]. Nasopharyngeal cancer is the ninth most common cancer in Indonesia [2].

The death of cancer patients is not only caused by cancer itself, but also several other factors such as the side effects of the given therapy. One of the side effects comes from cytostatic drugs. Cytostatic medicines have a very narrow margin of safety. It works by suppressing cell growth or cell proliferation and causing toxicity of normal tissue cells that divide rapidly [3]. According to the National Confidential Enquiry into Patient Outcome and Death, 4 of 10 patients who received chemotherapy got fatal side effects [4]. One of the fatal side effects is neutropenia (a subtype of leukopenia). Neutropenia is the highest hematological toxicity caused by chemotherapy treatment which has death as its final manifestation [5].

The number of leukocytes that decreases depends on the patient's condition such as the type of chemotherapy, the regimen, time, and the dose of cytostatic medicines used in the treatment. The lower the leukocyte count caused by cytostatic drugs in chemotherapy regimen decreases, the higher the possibility that the patient will have a neutropenic episode [6]. RSUP Dr. Hasan Sadikin Bandung is the top reference hospital in Province of West Java that has 60 new cases of nasopharyngeal cancer each year [2]. Therefore, this study compares three chemotherapy regimen in causing the decrease in leukocytes and the incidence of neutropenia in the patients with nasopharyngeal cancer in RSUP Dr. Hasan Sadikin Bandung.

METHODS

This study used analytic observational study with retrospective data collection and cross-sectional analytic design. The data were obtained from the medical records of inpatients with nasopharyngeal cancer at Dr. Hasan Sadikin General Hospital Bandung.

The inclusion criteria for this study were nasopharyngeal cancer patient data of Inpatient Unit at Dr. Hasan Sadikin General Hospital Bandung during January-December 2015, older than 18 years old, and had the determined chemotherapy regimen (cisplatin, cisplatin/5-fluorouracil [5-FU], and carboplatin/paclitaxel). Meanwhile, the exclusion criteria were incomplete or unreliable patient data, data of patients having regimen other than the aforementioned ones and/or patients with bone marrow (blood cell production) diseases.

Afterward, the data were analyzed using the ANOVA statistical method to compare the decrease in leukocytes between the three regimens, and using cross tabulation to compare the percentages of neutropenia cases between the three regimens. The results are shown in the description, tables, and graphics.

RESULTS AND DISCUSSION

Sorting chemotherapy regimen

Three regimens were chosen based on the nasopharyngeal cancer therapy guideline that is believed to be given the most to the nasopharyngeal cancer patients at Dr. Hasan Sadikin General Hospital Bandung. They are cisplatin (n=11), cisplatin/5-FU (n=9), and carboplatin/paclitaxel (n=7) with the total of 43 data at Depo Farmasi Pusat (Pharmacy). According to the NCCN Guidelines Version 1. 2015,

the three regimens are for nasopharyngeal cancer with status $T_1, N_{1-3}; T_2-T_4, N_{0-3}$ dan T_{1-4}, N_{0-3}, M_1 . Using number staging system, the regimens are for Stage III-IV cancer with or without metastatic.

Determining samples

The medical record of patients diagnosed (primary or secondary) with nasopharyngeal cancer at Inpatient Unit of Dr. Hasan Sadikin General Hospital Bandung in 2015 shows that there are 572 data, but only 88 meet the inclusion criteria. The details are as follows: 21 patients under 18 years old, 121 patients having the required regimen, and 33 patient data cannot be tracked.

The required components of the data included the patients' characteristics, the given regimen, the patients' leukocyte count before and after undergoing chemotherapy, and the patients' total/percentage of segmented neutrophils and band neutrophils. The next step was selecting the samples according to the theory and the requirements of the research.

Some data cannot be tracked due to inaccurate record, the absence of the patients' hematology test result, and the absence of information about the patients' regimen.

Data analysis

The samples of patient data were divided into three groups: 24 cisplatin data, 21 cisplatin/5-FU data, and 43 carboplatin/paclitaxel data.

In this part, the decrease in leukocytes, the average of absolute neutrophil count, and the number of neutropenia incidence comparison between the use of the three different chemotherapy regimens were analyzed with inferential analysis. Normality test was done first using Kolmogorov-Smirnov before the independent test. The results of the three regimens were normal.

Results of comparison among the regimens to the decrease in leukocytes

Data of cisplatin/5-FU regimen show that besides having the highest average number of the decrease in leukocytes, the regimen also causes the varied numbers (Table 1). It is likely caused by some other factors other than the regimen that affects the decrease in leukocytes such as drug dosage [6] and bone metastasis. Along with lungs and liver, bones are the most common sites to which nasopharyngeal cancer metastasizes [7] with 70-80% frequency of occurrence rate [8]. One of the effects of bone metastasis is a significant decrease in erythrocyte, thrombocyte, or leukocyte caused by decreased blood cell production [9]. In this research, it is found that there was 9.52% bone metastasis occurrence in the data of cisplatin/5-FU regimen. The results of homogeneity of variance test show that the most significant figure is 0.666 ($p>0.05$). Then, the result of F test shows that the average of the decrease in leukocytes is not significantly different which is 0.327 ($p>0.05$), although quantitatively different.

Basically, the three chemotherapy regimens have the risk of a decrease in leukocytes as a side effect. However, the possibility of the occurrence can be different from one regimen to another. For instance, cisplatin has gastrointestinal toxicity as the major side effect (90%) [10]. Some factors which are not included in the response of this study may be the reason that the results are not significant. Nevertheless, the three regimens can be said to be equal and safe enough as first-line therapy in patients with nasopharyngeal cancer Stage III-IV according to ANC average results.

Results of comparison among the regimens to ANC average

Similar to the previous comparison about the decrease in leukocytes, ANC comparison shows that cisplatin/5-FU likewise has the highest confidence interval and ANC average (Table 2).

Homogeneity of variance test shows homogeneous data result ($p>0.05$). The significant digit from F test is 0.240 ($p>0.05$). It

Table 1: The average of leukocyte decrease number

Regimens	n	Average (/mm ³)	Confidence interval	
			Lower limits	Upper limits
Cisplatin	12	2608.3	649.34	4567.32
Cisplatin/5FU	9	5255.6	1035.73	9475.38
Carboplatin/paclitaxel	23	3494.3	1871.54	5116.98
Total	44	3612.9	2393.12	4832.71

5-FU: 5-fluorouracil

Table 2: The average of ANC

Regimens	n	Average (/mm ³)	Confidence interval	
			Lower limits	Upper limits
Cisplatin	24	4625.0	3673.00	5576.1
Cisplatin/5-FU	21	6005.2	3566.07	8444.41
Carboplatin/paclitaxel	43	4338.1	3283.65	5392.53
Total	88	4814.2	4019.25	5609.11

5-FU: 5-fluorouracil

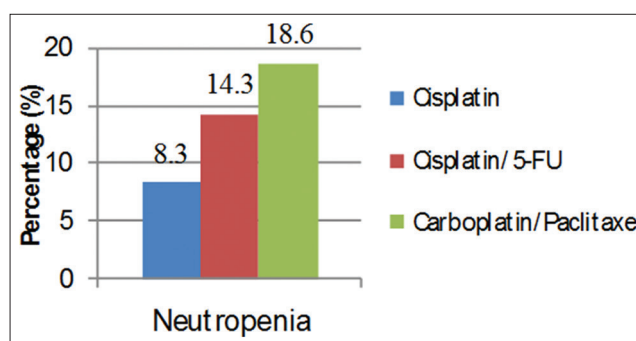


Fig. 1: The percentage of neutropenia incidence

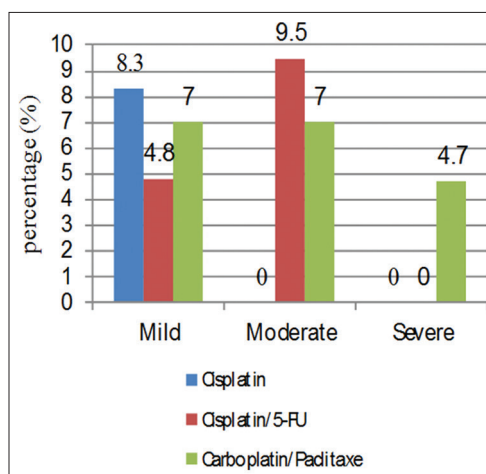


Fig. 2: The percentage of neutropenia's severity incidence

shows that they are no significant differences between the three regimens judging by the ANC average. Even though the differences are insignificant, the overall average of ANC is much higher than 1500 cells/mm³, which is normal limits of ANC. If the ANC average is lower than that, the patient is expected to have neutropenia. In addition to the results of decrease in leukocytes comparison,

it has been proven that the three regimens are safe enough from hematological toxicity.

Results of descriptive analysis of the regimens to the incidence rate of neutropenia

The incidence rate of neutropenia is important that it is frequently used in evaluating the use of chemotherapy drugs. The greater the percentage of the rate, the more unreliable the drug.

The analysis was begun by calculating the number of occurrences of neutropenia (patients whose ANC are <1500 cells/ m^3) in each regimen, then comparing them with the total of sample data. The result shows that regimen that has the smallest number of the incidence rate of neutropenia is cisplatin (8.3%) (Fig. 1). The graphic of neutropenia categorical data is obtained from the following details .

The data show that carboplatin/paclitaxel regimen tends to cause neutropenia more than the other regimens. Besides, the said regimen chart has severe neutropenia (2.3%) which does not exist in the other regimens (Fig. 2). Cisplatin/5-FU regimen's position is in the middle just like in the analysis of the decrease in leukocytes and ANC average, and it has the highest confidence interval. It proves that cisplatin/5-FU regimen has many other factors that influence the response of the therapy. Meanwhile, cisplatin regimen's tendency to cause neutropenia is the smallest among the three and mostly mild neutropenia.

It has been known that leukopenia (including neutropenia) and sensory neuropathy are common toxicity in the use of paclitaxel [11], while cisplatin's incidence rate of gastrointestinal toxicity is higher than 90% [10]. Then, cisplatin/5-FU regimen's side effects tend to be hematological and gastrointestinal toxicity [12].

CONCLUSION AND SUGGESTION

Conclusion

Based on the result of the study, it was concluded that there were no significant differences ($p>0.05$) between cisplatin, cisplatin/5-FU, and carboplatin/paclitaxel in the decrease in leukocytes, but cisplatin/5-FU regimen quantitatively has the highest ANC average and the largest decrease in leukocytes with varied leukocyte counts. Neutropenia incidence rates in descending order are carboplatin/paclitaxel, cisplatin/5-FU, and cisplatin.

Suggestion

Further studies that take drug dosage and hematological status of the patients right before and after chemotherapy into consideration are recommended. It is necessary to get the best result as an evaluation and consideration to decide treatment for patients with nasopharyngeal cancer Stage III-IV at Dr. Hasan Sadikin Bandung General Hospital.

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