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The Comparison Cellular Immunity Advanced Stage Nasopharyngeal Cell Carcinoma Patient Undergoing Chemotherapy Neoadjuvant 3 Cycle and its Connection with The Infection Event

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Abstract— **Introduction:** The chemotherapy will decrease the cellular immunity in nasopharyngeal carcinoma patient. The decrease of cellular immunity caused increasing infection event. Infection event in nasopharyngeal carcinoma inhibit the next cycle chemotherapy so the chemotherapy result become poorly. This study aimed to collect the data about cellular immunity post 3 cycle neoadjuvant chemotherapy, infection frequently and the difference decrease cellular immunity between infection group and non-infection group in advance nasopharyngeal carcinoma undergoing 3 cycle neoadjuvant chemotherapy. **Methods:** This research use before and after observasionaleksperimental, 1 group without control in 8th floor building A RSUPN Dr. CiptoMangunkusumo (RSCM), July – September 2015. Analyzed by bivariat by T or Mann Whitney Test. **Results:** There are decline cellular immunity, CD 4^{+} (p=0,002), CD 8^{+} (p=0,001). Ratio CD 4^{+}/CD 8^{+} in normal. 4 subject (29,4%) undergoing pneumonia, 1 subject (5,8%) undergoing oral mucositis and pneumonia. Non infection groups CD 4^{+} quantity are: 524,22; 408,11; 374,78; 296,78. Infection groups CD 8^{+} quantity are: 361,00; 280,00; 286,00; 218,00. Infection groups CD 8^{+} quantity are: 225,50; 361,00; 183,50; 168,00. **Conclusion:** The cellular immunity are decreased after 3 cycle neoadjuvant chemotherapy. Oral Mucositis and pneumonia are most frequently infection. There are a difference decrease cellular immunity between infection group and non-infection groups.

Keywords: Cellular immunity, neoadjuvant chemotherapy, pneumonia, oral mucositis.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy that is quite common in Indonesia and occupies the top five malignant tumors that are often found along with breast cancer, cervical cancer, lung cancer, and lymph nodes. Nasopharyngeal carcinoma is often found in Chinese and Asian populations with the highest incidence in China, namely 20 cases (100,000 population). In Indonesia the incidence rate of nasopharyngeal carcinoma is 4.7 - 6.4 cases and it is estimated that 7,000 - 8,000 new cases of nasopharyngeal cancer occur in Indonesia every year. The increasing number of cases of nasopharyngeal cancer usually occurs at the age of 40-50 years. [1-2]

Soetjipto's research at RSCM found that 50% of advanced nasopharyngeal carcinoma patients died 1 year after radiation. Susworo's research at RSCM which examined the results of radiation for 1 year found a one-year survival of stage 1 of 100%, stage 2 of 86.73%, stage 3 of 7.67% and stage 4 of 41.67%, this better result will have an impact in reducing hospitalization and mortality in nasopharyngeal carcinoma. Several factors contribute to the outcome of treatmentcarcinoma. The nasopharynx includes the general condition of the patient when undergoing chemotherapy and chemoradiation HB levels, the biological immune system of tumor cells, the degree of differentiation, and the histopathological types of the tumor, as well as the type and dose of chemoradiation drugs used. Cellular immune status is reported to affect the response of nasopharyngeal carcinoma to chemoradiation. On the other hand, chemotherapy and radiation administration will reduce cellular immunity in NPC patients. [1,2,3]

Approximately 75% of NPC sufferers have decreased cellular immunity. The decreased immune response in NPC sufferers can be caused by several factors such as internal factors (age, gender, etc.), production of various effective nasopharyngeal carcinoma cell processing materials suppression immune,and external factors such as chemotherapy and radiotherapy given.The reduced immune response in NPC sufferers is very detrimental because it provides opportunities for the growth of cancer cells and microbes in the body[15]. Research conducted by Xiao[16] on 229 nasopharyngeal cancer undergoing chemoradiation obtained a comparison of 5 year overall survival. in men:women by 72.2% : 96% where p = 0.001 which proves the results of NPC treatment in female patients are better than male patients.In addition to the gender factor, cellular immunity is also influenced by age, with increasing age, the cellular immune response will decrease, so that the body's ability to fight infection and fight against the development of cancer cells will decrease.Hirokawa's research[16] which linked age to sex and cellular immunity showed that cellular immunity decreased with age and there were differences between men and women where the decrease in cellular immunity in women was slower than in men. Nutritional status also plays an important role in determining the cellular immune response. Chandra's research[17] proves that malnutrition will cause disturbances in various aspects of immunity, including phagocytosis, cell proliferation responses to mitogens, and cytokine production by lymphocytes.Depression is also common in patients with nasopharyngeal carcinoma. Miller's research[27] proved that depressed patients will find a decrease in the number and function of NK cells. NK cells play a role in phagocytosis of cancer cells by the presence of granules in the cytoplasm of NK cells that are capable of lysing cancer cells.

Chemotherapy as an anti-cancer drug in nasopharyngeal carcinoma has the effect of inhibiting proliferation and inducing cancer cell death through the mechanism of apoptosis. However, it can cause unwanted effects, namely myelosuppression. Like radiotherapy, chemotherapy can also cause damage to immunological cells which has an effect on decreasing immunity, especially cellular immunity. [4,5,6,7,8.]

Until now there has been no research in Indonesia that examines cellular immunity in nasopharyngeal cancer patients receiving Neoadjuvant chemotherapy. Several studies prove the existence of features of cellular immunity in patient with carcinoma nasopharynx who have undergone radiotherapy but this may not describe the same results when performed on patientsnasopharyngeal carcinoma who underwent chemotherapyNeoadjuvant. [7,8,9]

Study of the picture of the patient's cellular immunitynasopharyngeal carcinoma advanced stage pre and post chemotherapyNeoadjuvant and the frequency of post-chemotherapy infections is expected to increase doctors' attention to the problem of decreased cellular immunity before and after being given chemotherapy as well as the possibility of lung infections and tumor areas that will appear if the decrease in cellular immunity results in an increase in the incidence of infection. Of course, it is necessary to evaluate the infection assessment before and after chemotherapyNeoadjuvant and consideration of giving *G-CSF (Granulocyte Colony Stimulating Factors)* in each chemotherapy cycle. G-CSF is a cytokine that stimulates the production of granulocytes. G-CSF administration in humans will result in increased circulating neutrophils and reduced transit time from stem cells to mature neutrophils. so that G-CSF is indicated for administration in cancer patients who experience neutrophenia after chemotherapy. [7-8]

2. Methods

The study used a one-group Before and After intervention study using a group without a control which was a quasi- or quasi-experimental study. The location of the research was in the inpatient installation of building A, 8th floor of RSCM from July to September 2015 (3 months). The target population is all advanced nasopharyngeal carcinoma patients who will undergo cytostatic chemotherapy at RSCM while the

affordable population is advanced nasopharyngeal cancer patients who will undergo chemotherapy.Neoadjuvant III cycle before chemoradiation at RSCM.

The inclusion criteria of the population are having an age range of 17 to 70 years, patients with nasopharyngeal carcinoma stage 3 and 4 (advanced stage), have a performance status: ECOG 0-1,chemotherapy naive and will get neoadjuvant chemotherapy three cycles (given DPJP in the inpatient room).

The study was conducted with patient consent whereby each patient who met the inclusion criteria was planned to participate in the study. Procedure The study was carried out by taking a 10 ml blood sample in patients with advanced nasopharyngeal carcinoma in the median cubital vein. Of the 10 ml blood sample, 6 ML was used for CD 4^+ and CD 8^+ examination, while the remaining 4 ML blood was used for complete blood counts such as HB, leukocytes, platelets, erythrocytes, hematocrit, and leukocyte count. NPC patients who will undergo neoadjuvant chemotherapy are assessed for cellular immune response by examining CD 4^+ and CD 8^+ lymphocytes. Every cycle of chemotherapyNeoadjuvant, Cellular immune response was assessed again by examination of $CD4^+$ and CD 8^+ lymphocytes. After neoadjuvant chemotherapy, an assessment of the presence of infection in the KNF patient was carried out, either an airway infection or an infection in the tumor area.

Decreased primary and secondary cellular immunity after 3 cycles of Neoadjuvant chemotherapy was performed using bivariate analysis with the Witney men's test. In this study will be seen whether the decrease in cellular immunity will increase the incidence of post-3 cycle neoadjuvant chemotherapy infections and whether the decrease in cellular immunity will increase. This study uses a significance level of 0.05 with a 95% confidence interval.

3. Results

This study was followed by 17 subjectsnamely advanced nasopharyngeal carcinoma patients (NPC) who underwent 3 cycles of Neoadjuvant chemotherapy and met the inclusion criteria. Cellular immune response was examined before and after each cycle of chemotherapy and at the end of 3 cycles of neoadjuvant chemotherapy to see its relationship with the incidence of infection. It was found that 12 research subjects were male and 5 subjects were female, the age of the research subjects was between 22 - 57 years with a median age of 46.7 years, this is in accordance with the theory that NPC affects many people aged 25 - 60 years with peak age between 45-54 years.

Table 3.1 Results of cellular immunity after 3 cycles of neoadjuvant chemotherapy

Variable	**Neodjuvan prechemotherapy**		**Post Chemotherapy Cycle 1**		**Post Chemotherapy Cycle 2**		**Post Chemotherapy Cycle 3**	
	Total/mm^3	Range value	Total/mm^3	Range value	Total/mm^3	Range value	Total/mm^3	Range value
CD 4^{+x}	403.4	290-562	307.2	222-392	307.4	241-373	258	200-316
CD 8^{+x}	293	222-363	225.6	169-282	229.12	185-273	203.3	163-243
Ratio	1.37		1.36		1.34		1.30	

Table 3.2 Decreased cellular immunity after 3 cycles of neoadjuvant chemotherapy

Variable	Group		*P*
	Pre	Post	
CD 4^+	403.41 (220.2)	258.4 (113,2)	0.002
CD 8^+ Median (min – max)	293 (222-363)	203 (163-243)	0.001

This examination of CD 4^+ and CD 8^+ illustrates cellular immunity. This study found that the average CD 4^+ was low before chemotherapy and decreased after the third Neoadjuvant chemotherapy cycle (p=0.002), while the average CD 8^+ value also decreased after the third Neoadjuvant chemotherapy (p=0.001), although there was a decrease in the number of CD 4^+ and CD 8^+, but the ratio of CD 4^+/CD 8^+ is still within normal limits. It is very likely that the low CD 4^+ average before chemotherapy is caused by various internal and external factors. This shows that the cellular immunity of patients with advanced nasopharyngeal carcinoma is already low before chemotherapy is started. This needs special attention because after 3 cycles of Neoadjuvant chemotherapy the average value of CD 4^+ and CD 8^+ decreased even though the patient will then undergo chemoradiation.

Table 3.3 Incidence of infection after 3 cycles of neoadjuvant chemotherapy

Clinical Developments	Total	Percentage
No Infection was found	9	52.9
Found infection	8	47.1

Table 3.4 Frequency of infection after 3 cycles of neoadjuvant chemotherapy

Infection Incident	Total	Percentage
Oral Mucositis	4	23.6
Pneumonia	3	17.7
Oral Mucositis and Pneumonia	1	5.8

Based on the results of the table after 3 cycles of Neoadjuvant chemotherapy, the incidence of infection in the form of oral mucositis and pneumonia was in 8 patients (47.1%) with details of oral mucositis experienced by 4 patients (23.6%), pneumonia experienced by 3 patients (17.7%), also lung infection and tumor area were found in 1 patient (5.8%). Research according to Cawley which proves that 15-40% of patients who receive adjuvant chemotherapy have a toxic effect on the oral mucosa. Another study by Lalla proved that nasopharyngeal carcinoma patients undergoing adjuvant Cisplatin 5 FU chemotherapy had an incidence of oral mucositis of 22-51%. Sufiawati's research examined patients with nasopharyngeal carcinoma undergoing adjuvant chemotherapy, 20-40% experienced oral mucositis, this figure increased by 80-90% when radiation was performed. Oral mucositis appears due to the effects of chemotherapy, especially in rapidly dividing cells such as skin and mucosal cells, hair, blood, ova and sperm. Oral mucositis can affect the patient's quality of life, increase the risk of infection, delay chemotherapy, and even therapy failure in cancer patients. [11,12]

This study also found that 17.7% of research subjects had lung infections. According to Guo's research in China, in nasopharyngeal carcinoma patients undergoing neoadjuvant chemotherapy, getting pneumonia is a side effect that is often found besides oral mucositis and diarrhea, the incidence of pneumonia is increasing, especially in patients who experience neutropenia. another study conducted by Chi and others in China in

patients with advanced nasopharyngeal carcinoma who received pneumonia is an infection that is often found in nasopharyngeal carcinoma patients undergoing adjuvant chemotherapy other than mucositis, gastrointestinal infections, reactivation of hepatitis and cardiovascular disease. It can be seen that the frequency of oral mucositis did not differ between adjuvant and neoadjuvant chemotherapy. Meanwhile, the incidence of pneumonia with neoadjuvant chemotherapy is lower than that of adjuvant chemotherapy. [13,14]

Table 3.5 The mean of CD 4^+ and CD 8^+ in the infected group in each cycle of chemotherapy 1,2,3

Variable	Group			
	Pre	Post 1	Post 2	Post 3
CD 4^+, Mean	247.00 (SB 165.52)	194.88 (SB 109.87)	231.63 (SB 129.47)	215.25 (SB 1018.42)
CD 8^+, Median	225.5 (108-515)	361 (89-513)	183.5 (128-380)	168 (122-326)

Table 3.6 The mean of CD 4^+ and CD 8^+ in the uninfected group in each chemotherapy cycle1,2,3

Variable	Group			
	Pre	Post 1	Post 2	Post 3
CD 4^+, Mean	542.44 (SB 163.72)	408.11 (SB 141.05)	374.78 (SB 86.38)	296 (SB 108.85)
CD 8^+, Median	361.0 (89-513)	280 (86-465)	286 (84-368)	218 (82-376)

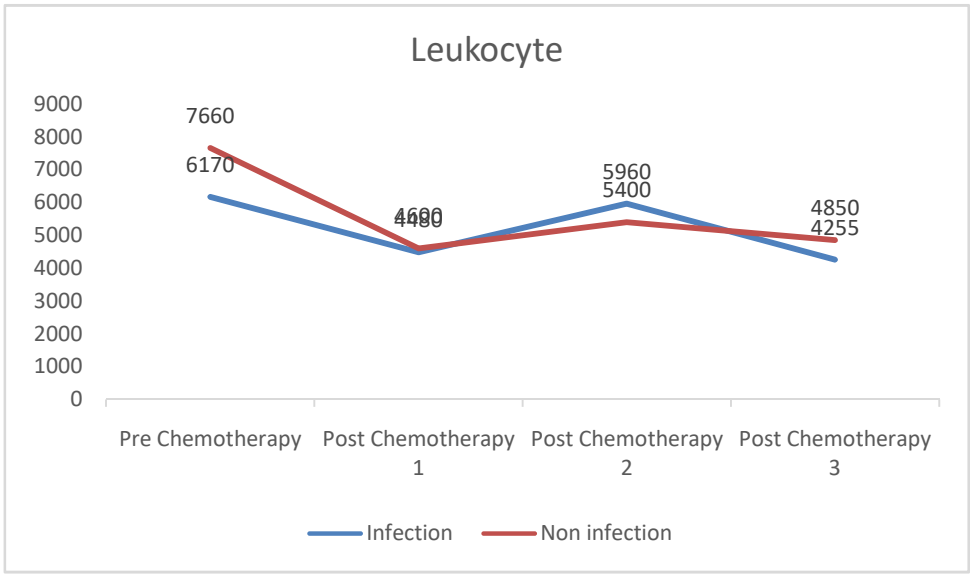
Table 3.7 Differences in decreased cellular immunity between infected and non-infected advanced nasopharyngeal carcinoma patients after 3 cycles of neoadjuvant chemotherapy

Variable	Infection		P
	Yes	No	
Delta CD 4^+	-31.75 (SB 106.68)	-245.66 (SB 136.07)	0.003
Delta CD 8^+	-52.25 (SB 62.70)	-123.44 (SB 83.45)	0.068

In the uninfected group the CD 4^+ count was normal before chemotherapy Neoadjuvant and decreased below normal after chemotherapy neoadjuvant. In the infected group the CD count was 4^+ it has been below normal since before 3 cycles of neoadjuvant chemotherapy and it has fallen below normal after chemotherapy Neoadjuvant 3 cycles. Low 4^+ CD count before chemotherapy increases the potential for infection during and after chemotherapy. In the infected group, the CD 8^+ count decreased during advanced nasopharyngeal carcinoma patient stage of chemotherapy Neoadjuvant 3 cycles. Even so after chemotherapyNeoadjuvant After 3 cycles, the CD 8^+ count in the uninfected group was still above normal, whereas in the infected group the CD 8^+ count was normal before neoadjuvant chemotherapy and decreased below normal after 3 cycles of neoadjuvant chemotherapy.

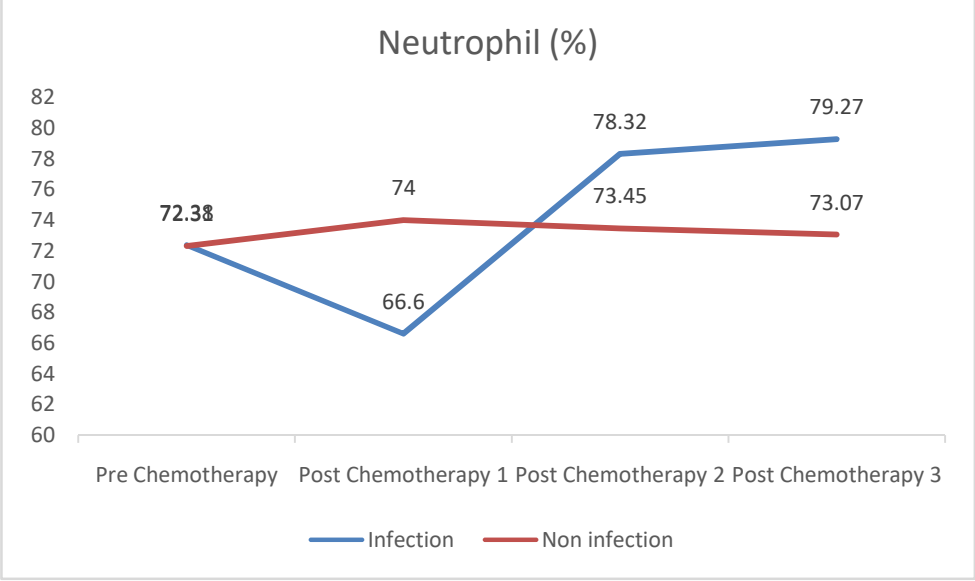
From the results of examination of the number of CD 4^+ and CD 8^+ in advanced nasopharyngeal carcinoma patients undergoing chemotherapy Neoadjuvant In 3 cycles, there was a difference in decreased cellular immunity between infected and uninfected patients, where in the uninfected group, cellular immunity was still normal before chemotherapy Neoadjuvant and decreased below normal after chemotherapy Neoadjuvant 3 cycles. Meanwhile, in the infected group, cellular immunity was already low below normal before chemotherapy and will further decrease below normal after 3 cycles of Neoadjuvant chemotherapy.

Table 3.8 Median change in leukocyte count in every cycle of neoadjuvant chemotherapy



The number of leukocytes in both the infected and uninfected groups before chemotherapy Neoadjuvant In 3 cycles there were 6170 infected patients and 7660 uninfected patients. At the first post chemotherapy Neoadjuvant, the number of leukocytes decreased in the infected group by 4,480 and in the uninfected group by 4,600. At the second post chemotherapy Neoadjuvant leukocyte counts increased in the infected group by 5,960 and in the uninfected group by 5,400. At the third post neoadjuvant chemotherapy the number of leukocytes decreased in the infected group to 4255 and in the uninfected group to 4850. There were no signs of leukopenia (leukocyte count <4000) in both the infected and uninfected groups of advanced nasopharyngeal carcinoma patients undergoing 3 cycles of neoadjuvant chemotherapy.

Table 3.9 Median change inneutrophil count in every cycle of neoadjuvant chemotherapy



From the graphic, the percentage of neutrophils in the patient with carcinoma advanced nasopharynx who underwent Neoadjuvant chemotherapy 3 cycles before being normal in the infected group were 72.38% and

72.31% for the uninfected group. Neutrophil percentage at the first post-chemotherapy neoadjuvant decreased in the infected group (66.6%) while the uninfected group tended to increase to 74%. Neoadjuvant chemotherapy cycle 2 in the infected group increased to 78.32% while in the uninfected group it tended to decrease to 73.45%. At the third cycle of post chemotherapy neoadjuvant in the infected group it increased by 79.27% and in the uninfected group it decreased to 73.07%.

The number of leukocytes and neutrophils appeared normal at the start of chemotherapy and there was no decrease significantly in each cycle of neoadjuvant chemotherapy there were no signs of leukopenia and neutropenia in advanced nasopharyngeal carcinoma patients undergoing 3 cycles of neoadjuvant chemotherapy. This result is not in accordance with previous research, such as Kong's study, found degrees of 3-4 myelosuppression in nasopharyngeal carcinoma patients after cycle 3 of neoadjuvant chemotherapy. Meanwhile, Lee's research found myelosuppression in 27% of post-chemotherapy patients driving the first cycle, and in the third post cycle of chemotherapy driving there were 78% of patients experienced myelosuppression. The absence of leukopenia and neutropenia in this study needs to be evaluated, especially when sampling leukopenia and neutropenia usually occur on day 7 - 14. Sampling in this study was carried out on day 7 and day 14. Leukopenia and neutropenia did not occur because leukopenia or neutropenia actually did not occur, or leukopenia and neutropenia occurred between days 7-14 when the patient was at home.[10,11]

4. Conclusion

There is a decrease in cellular immunity quantitatively after administration of neoadjuvant chemotherapy in advanced stage NPC patients compared to before administration of chemotherapy.In patients with quantitatively decreased cellular immunity there was a high incidence of infection where the infections that occurred were oral mucositis in 4 subjects (23.6%), pneumonia in 3 subjects (17.7%), oral mucositis and pneumonia in 1 subject (5.8%) post chemotherapyNeoadjuvant 3 cycles.Thereis a difference in decreased cellular immunity between infected and non-infected patients in advanced nasopharyngeal carcinoma patients after 3 cycles of neoadjuvant chemotherapy.

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