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RESEARCH ARTICLE

ANALYSIS OF MEAN PLATELET VOLUME IN NASOPHARYNGEAL CARCINOMA PATIENTS UNDER CHEMOTHERAPY AT HAJI ADAM MALIK GENERAL HOSPITAL MEDAN IN 2015-2017

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ABSTRACT

Background: The mean value of Mean Platelet Volume (MPV) is a valid parameter in the diagnosis and management of various types of cancer for many years. An increase in MPV may become a significant biomarker of head and neck malignancies, also a warning of thrombosis risk in malignancy, while decreased MPV is related to the administration of chemotherapy.
Aim: This study aimed to determine MPV values in patients with nasopharyngeal carcinoma (NPC) pre and post chemotherapy based on types of chemotherapy and histopathology.
Materials and Methods: Analytic study with a retrospective cohort design was carried out at H. Adam Malik General Hospital, Medan. Data were collected using secondary data on medical records of patients with pre and post chemotherapy nasopharyngeal carcinoma from January 2015-December 2017 in the form of demographic, clinical, histopathological and chemotherapy data. Data were processed descriptively and analyzed by ANOVA test.
Results: MPV levels in NPC with histopathology of Keratinizing Squamous Cell Carcinoma (SCC) were fluctuating, while for Non-Keratinizing SCC and Undifferentiated Ca. MPV levels exhibited a downward trend. Regardless of the type of histopathology, decreased MPV levels occurred significantly in concomitant, neoadjuvant and full-dose chemotherapies, with the greatest decrease in concomitant.
Conclusion: MPV value might be favorable to be used as a prediction parameter for chemotherapy response and therapeutic efficacy of chemotherapy to be administered.

Key words: Mean platelet volume, Nasopharyngeal carcinoma, Chemotherapy, Histopathology.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one of the head and neck malignancies, endemic in Southeast Asia and has a low survival rate for sufferers (Tang *et al.,* 2016). Most cancer patients often experience some hematological problems. Some of these problems can be directly related to primary or secondary diseases due to the modality of management administered (Cihan, 2015). The mean value of Mean Platelet Volume (MPV) is a valid parameter in the diagnosis and management of various types of cancer for many years, and studies that investigate the relationship between these parameters and cancer are still limited. Although it is the most common malignancy found in the head and neck, there is still a lack of clinically proven biomarkers in the diagnosis and prognosis of head and neck malignancies, and to date no serum biomarkers are well known in the diagnosis of nasopharyngeal carcinoma. There are no studies investigating the relationship between blood parameters such as MPV against nasopharyngeal carcinoma and changes in MPV values after chemotherapy in patients with nasopharyngeal carcinoma (Cihan *et al.,* 2015). An increase in MPV can be a significant biomarker of head and neck malignancies and a warning of the risk of thrombosis in malignancy. Thrombosis increases in head and neck malignancies have been reported in several studies (Paneesha, 2010). A study in Korea revealed that groups of liver cancer patients with layered squamous cell types had higher MPV levels than the normal control group (Zhang, 2016). Keles et al. in his study of patients with renal cell carcinoma found an increase in mean MPV values along with the higher stage of kidney cancer suffered (Keles *et al.,* 2014). Ferroni et al. conducted a study of MPV values for 589 patients of various solid cancers and discovered a decrease in MPV values during the first 3 months of chemotherapy and MPV values returned to normal limits at the end of chemotherapy (Ferroni, 2014).

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This decrease in MPV values was related to chemotherapy drugs administered. Similar study is still rarely carried out in other countries. This study aimed to determine MPV values in patients with nasopharyngeal carcinoma pre and post chemotherapy based on the type of chemotherapy and histopathology, so that it might be used as a predictive parameter of chemotherapy response and therapeutic efficacy of chemotherapy to be administered, related to survival rates.

MATERIALS AND METHODS

This analytic study with a retrospective cohort design was carried out in the Division of Oncology-Head Neck Surgery, Department of Otorhinolaryngology, H. Adam Malik Hospital, Medan. Data were collected using secondary data on medical records of patients with pre and post chemotherapy nasopharyngeal carcinoma from January 2015 - December 2017. The sample inclusion criteria were complete patient medical records and comprising all the data needed, namely: personal data, laboratory results include pre and post chemotherapy MPV values per cycle along with histopathological findings. Exclusion criteria were samples with a history of cardiovascular disease, myeloproliferative conditions, rheumatoid arthritis, thyrotoxicosis, history of splenectomy, and antiplatelet use. This situations were known to cause an increase in MPV value. In this study, independent variables included histopathology type; keratinizing squamous cell carcinoma (SCC), non-keratinizing SCC, and undifferentiated in nasopharyngeal carcinoma patients, while the dependent variable was MPV value. NPC was diagnosed based on histopathological examination of biopharyngeal biopsy by anatomical pathology laboratories. MPV was calculated using the formula

MPV (fl) = Pct (%) x1000: Plt (x103/µl).

where Plt was the platelet count and Pct was plateletcrit, which was the amount of blood volume containing platelets in percent, calculated electronically from histogram data. The used reference range for the normal MPV was 7.0 - 10.2 fl. Clinical stage was defined using the TNM staging system based on nasopharyngeal contrasted CT-scan results recorded in medical records according to the 2016 AJCC/UICC (American Joint Committee on Cancer/ International Union Against Cancer). The histopathology type was taken from a biopsy tissue or the result of surgery and was seen under a microscope by a pathologist and recorded in the medical record. The histopathology was divided into 3 types based on WHO 1978 namely keratinizing squamous cell, non-keratinizing squamous cell, and undifferentiated. Data were collected using the master table. Quantitative data that was the MPV value were described using the mean and SD. To find out the difference in MPV values before and after chemotherapy for each cycle, normality test was performed with Kolmogorov-Smirnov. Normal data were tested using ANOVA, and otherwise with Kruskal Wallis test. Results with $p < 0.05$ were considered as statistically significant.

RESULTS

Based on gender characteristic, the majority of subjects were male as many as 99 subjects (71.7%), while female subjects amounted to 39 (28.3%). The majority of study subjects aged 40-49 years were 39 (28.3%), followed by the age group of 50-59 years as many as 31 (22.5%). The least age group was 4 subjects aged 70-79 years (2.9%). Based on the results of histopathological examination, the most types of NPC were Non-Keratinizing SCC as many as 91 (65.9%), followed by Undifferentiated types as many as 30 (21.7%) and Keratinizing SCC as many as 17 (12.3%). The majority of study subjects as many as 75 (54.3%) were stage IV NPC patients, followed by 63 NPC patients with stage III.

Table 1. Frequency distribution based on characteristics

Characteristics	N = 138	%
Gender		
Male	99	71,7
Female	39	28,3
Age (years)		
<20	7	5,1
20-29	13	9,4
30-39	24	17,4
40-49	39	28,3
50-59	31	22,5
60-69	20	14,5
70-79	4	2,9
Histopathology		
KSCC	17	12,3
NKSCC	91	65,9
Undiff Ca	30	21,7
Stadium		
III	63	45,7
IV	75	54,3
Total	138	100

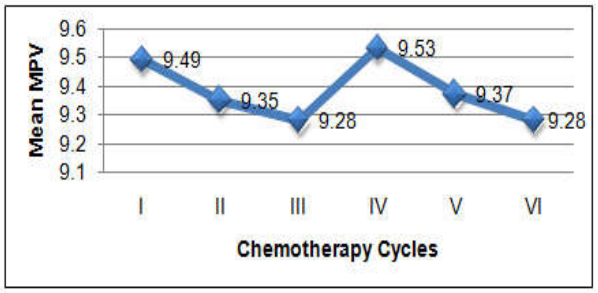

Figure 1. Changes in MPV levels during administration of chemotherapy in Keratinizing SCC subjects

As seen in Figure 1, MPV levels in Keratinizing SCC totaling 17 subjects during the chemotherapy cycle were shown. The mean MPV levels were fluctuated. Cycles II and III showed a decrease but the cycle IV slightly rose then continued to fall back in cycle V until cycle VI. The highest mean MPV level was in the cycle I with a mean of 9.49 (SD = 0.98) and the lowest was in cycle VI with a mean of 9.28 (SD = 0.85). it should be: the cycle IV greatly increase then continued to fall back in cycle V until cycle VI. The highest mean MPV level was in the cycle IV with a mean of 9.53 (SD = 0.95) and the lowest was in cycle VI with a mean of 9.28 (SD = 0.85).

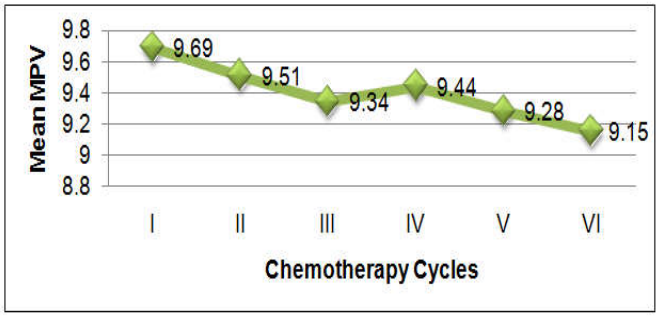

Figure 2. Changes in MPV levels during administration of chemotherapy in Non-Keratinizing SCC subjects

MPV levels in Non-Keratinizing SCC, amounting to 91 subjects during the chemotherapy cycle, were shown in Figure 2. The mean MPV levels showed a downward trend. In cycle IV, it slightly rose and went back down in cycle V until cycle VI. The highest mean MPV level was in cycle I with a mean of 9.69 (SD = 0.82) and the lowest was in cycle VI with a mean of 9.15 (SD = 0.82).

found that the greatest decrease in MPV levels was in the full-dose type of chemotherapy, with a mean decrease of 0.38 (SD = 0.33), followed by neoadjuvant at 0.28 (SD = 0.36), and the smallest decrease was found in concomitant chemotherapy with a decrease of 0.21 (SD = 0.38). The results of the analysis using the ANOVA test showed the mean decrease in MPV of the three types of chemotherapy was not significantly different (p = 0.738).

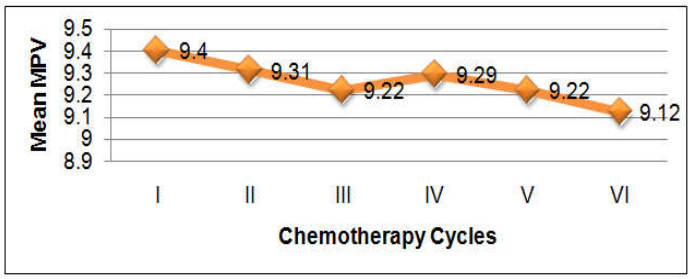

Figure 3. Changes in MPV levels during administration of chemotherapy in Undifferentiated subjects

Table 2. Difference in changes of MPV levels in Keratinizing SCC, Non-Keratinizing SCCand Undifferentiated histopathologybased on chemotherapy

Chemotherapy	n	Delta MPV, mean (SD)	p	Post Hoc	
				Concomitant	Neoadjuvant
Keratinizing SCC					
Full-dose	5	0,16 (0,47)	0,747[a]		
Concomitant	4	0,30 (0,18)			
Neoadjuvant	8	0,2 (0,12)			
Non Keratinizing SCC					
Full-dose	10	0,45 (0,44)	0,001[b]	0,026[c]	0,948[c]
Concomitant	27	0,74 (0,32)			<0,001[c]
Neoadjuvant	54	0,46 (0,30)			
Undifferentiated					
Full-dose	5	0,38 (0,33)	0,738[a]		
Concomitant	7	0,21 (0,38)			
Neoadjuvant	18	0,28 (0,36)			

[a]ANOVA, [b]Kruskal Wallis,[c]Mann Whitney

MPV levels in Undifferentiated Ca subjects totaling of 30 during the chemotherapy cycle were shown in Figure 3. The mean MPV levels showed a downward trend. In cycle IV, it slightly rose and went back down in cycle V until cycle VI. The highest MPV level was found in cycle I with a mean of 9.40 (SD = 0.70) and the lowest was in cycle VI with a mean of 9.12 (SD = 0.80). In patients with Keratinizing SCC, the greatest decrease in MPV level was found in concomitant chemotherapy, with a mean decrease of 0.30 (SD = 0.18), followed by neoadjuvant at 0.20 (SD = 0.12), and the smallest was full-dose chemotherapy with a decrease of 0.16 (SD = 0.42). The results of the analysis using the ANOVA test showed the mean decrease in MPV of the three types of chemotherapy did not differ significantly (p = 0.747).

In patients with Non-Keratinizing SCC histopathology, the greatest decrease in MPV level was found in concomitant chemotherapy, with a mean decrease of 0.74 (SD = 0.32), followed by neoadjuvant at 0.46 (SD = 0.30), and the smallest decrease was in the full-dose chemotherapy with a decrease of 0.45 (SD = 0.44). The results of the analysis using the Kruskal-Wallis test showed that the mean MPV reduction of the three types of chemotherapy was significantly different (p = 0.001). The results of the follow-up analysis showed that the mean change in MPV levels in the concomitant type was significantly different compared to the full-dose (p = 0.026) and neoadjuvant (p = <0.001). In patients with histopathological type of Undifferentiated Carcinoma, it was

DISCUSSION

In this study it was found that dominant gender of NPC patients was male. Several studies in various countries also showed that there were male NPC sufferers than females (Lin *et al.,* 2003). This was predicted to be correlated with life and work habits. In this study, the highest frequency of age distribution of NPC patients was 40-49 years. This could be due to a decrease in endurance in the elderly so that malignancy often occur. In this study the clinical stage distribution of NPC patients with the highest frequency was stage IV. Early symptoms of NPC are not typical, similar to upper respiratory tract infections so that attention from patients and examiners are deviated. In addition, the locations of tumors hidden in the nasopharynx, difficulty to examine, inadequate equipment, lack of proper knowledge, fear of doctor visit, and weak socioeconomic conditions of sufferers are often being the obstacles in making a diagnosis of this disease. Therefore early symptoms are often overlooked and patients are diagnosed after an advanced stage. In this study it was found that the distribution of histopathological types of patients with the highest frequency of NPC were non-keratinizing squamous cell carcinoma followed by undifferentiated and keratinizing squamous cell carcinoma. This finding was similar to several studies that discovered that the proportion of histopathological types of non-keratinizing squamous cell carcinoma (NKSCC) and undifferentiated carcinoma were found mostly in endemic areas. While

keratinizing squamous cell carcinoma (KSCC) tended to be higher in non-endemic areas. Several studies had reported that KSCC had a 25% incidence in NPC patients in North America, but only around 1% in endemic areas, while NKSCC and undifferentiated carcinoma account for 95% of cases in high incidence areas, but around 60% in North America (Tabuchi, 2011). Of all subjects regardless of histopathology type of NPC, it was found that the greatest decrease in MPV levels was found in concomitant chemotherapy, followed by neoadjuvant and the smallest decrease was found in the full-dose chemotherapy. Until now, there have been no studies investigating the relationship between blood parameters such as MPV to NPC and changes in MPV values after chemotherapy in NPC patients, but Bilir et al. in his study of 47 patients with gastric cancers treated with chemotherapy regimens (25) found a significant reduction in MPV values in the mid-cycle of chemotherapy (from 8.1 fl to 7.7 fl) and decreased at the end of the chemotherapy cycle (from 7.7 fl to 7.4 fl). While 22 other patients treated with radiation had no significant decrease in MPV values, but platelet counts decreased significantly. They concluded that the chemotherapy modality could reduce MPV levels but had no effect on radiotherapy modalities (Bilir, 2013). MPV values correlate with malignant patient characteristics where high MPV values express PDGF, thromboxane A2, excessive glycoprotein Ib and IIb/IIIa receptors which can increase the occurrence of thrombosis and growth rate and invasion of malignant tumors, markers of angiogenesis, metastasis and proteolysis in the inflammatory process of malignancy and be a prognostic factor (Inagaki, 2014 and Sehitoglu, 2016). MPV can be used as a marker of angiogenesis in patients with malignancy due to the role of platelets as angiogenic, metastatic and proteolytic in the process of inflammatory malignancy. Procoagulant-releasing tumor cells, fibrinolytic factors, mediators, proteases, cytokines, which have a direct effect on platelet production and activation and directly interact with thrombosis through adhesion molecules (Noble, 2010 and Bagoly, 2015). Some diseases such as malignancies that affect platelet counts, can cause disruption in platelet volume and function. Along with increased platelet reproduction, MPV which is a significant hemostatic physiological variable also increases. A number of platelets that become reactive cause an increase in the number of prothrombic factors and accumulations that are known to cause microvascular and macrovascular pathology in malignant patients.

The results of study conducted by Lian et al. found that gastric cancer patients who had low MPV values improved the response to chemotherapy (Lian, 2015). Ferroni et al. conducted a study of MPV values for 589 patients of various solid cancers and discovered a decrease in MPV values during the first 3 months of chemotherapy and MPV values returned to normal limits at the end of chemotherapy. More than 90% of patients had chemotherapy every month with each cycle of 28 daysof administrations (Ferroni *et al.,* 2014). Chemotherapy, especially platinum-based compounds, has a role in reducing MPV values during treatment. This decrease in MPV values is related to chemotherapy drugs administered, where platinum-based compounds have the strongest correlation. Provision of various anti-neoplastic drugs can cause platelet defects, including platinum analogues. Several mechanisms related to decreased MPV values due to the administration of platinum-based chemotherapy include disorders of the signal protein kinase C and impaired circumferential microtubule rings that are responsible for platelet contraction, centralization of platelet secretory granules and platelet degranulation. In addition to these direct effects, other indirect effects associated with decreased MPV values during chemotherapy include chemotherapy-induced bone marrow hypoplasia as well as the inflammatory status that accompanies cancer and its treatment. In this case, tumor necrosis-alpha levels (TNF-α) have been shown to increase after the first 2 cycles of platinum-based chemotherapy. TNF-α has been shown to trigger platelet activation, while other inflammatory cytokines can affect megacaryocytopoiesis and thrombocyte volume. In this study, the Keratinizing SCC histopathology group exhibited that the mean MPV levels were quite fluctuated. For Non-Keratinizing SCC and Undifferentiated Ca histopathology groups, it was proven that the mean MPV levels showed a downward trend. To date, there is still no literature explaining the relationship between NPC histopathology types and changes in MPV values in concomitant, neoadjuvant and full-dose chemotherapies. However, this study discovered the greatest decrease in MPV values was obtained in concomitant chemotherapy administration, on the histopathologic type of Keratinizing SCC, Non-Keratinizing SCC and Undifferentiated Carcinoma. In addition, this study found that in the Non-Keratinizing SCC histopathology, the mean changes in MPV values were significantly different ($p = 0.001$) against concomitant chemotherapycompared to full-dose ($p = 0.026$) and neoadjuvant ($p = < 0.001$), but the mean changes in MPV value was not significantly different in the histopathology type of Keratinizing SCC and Undifferentiated Carcinoma. These findings yielded the assumption that concomitant chemotherapy was best administered to NPC patients with Non-Keratinizing SCC histopathology compared to the other two types, despite the absence of literature that explained in detail the exact underlying mechanisms.

Conclusion

MPV levels in NPC with histopathology of Keratinizing SCC were fluctuated, while for Non-Keratinizing SCC and Undifferentiated Ca, MPV levels exhibited a downward trend. Regardless of the type of histopathology, decreased MPV levels occurred significantly in concomitant, neoadjuvant and full-dose chemotherapies, with the greatest decrease in concomitant chemotherapy. MPV value might be favorable to be used as a prediction parameter for chemotherapy response and therapeutic efficacy of chemotherapy to be administered.

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