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Correlation Between Superoxide Dismutase Serum Level Alteration with Neck Metastatic Tumor Post Cisplatin–Paclitaxel Chemotherapy Response in Nasopharyngeal Carcinoma Patients

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Abstract Nasopharyngeal carcinoma (NPC) is a malignant tumor in the nasopharynx. The patients treated with neoadjuvant combination chemotherapy cisplatin–paclitaxel while waiting a radiotherapy. This combination can produce a very high reactive oxygen species (ROS) level. Our body has a protective mechanism against oxidant through superoxide dismutase (SOD) that can inhibit DNA chain damage from ROS induction produced by chemotherapy in NPC patients. This study aimed to analyze the correlation between SOD level alteration with neck metastatic tumor response after cisplatin–paclitaxel chemotherapy. This was a cohort study. Thirty samples examined for neck metastasis tumor volume (VTM) and serum SOD were examined with ELISA pre- and postchemotherapy. Statistical significance was defined as $p < 0.05$. Mean SOD serum level pre-chemotherapy and post-chemotherapy were 179.5 and 209.1, respectively. Mean tumor metastatic volume pre and post chemotherapy were 127.3 and 62.7, respectively. The correlation test with the result (r) 0.180 and $p = 0.340$. There was no correlation between SOD serum level alteration with VTM volume post cisplatin–paclitaxel chemotherapy in NPC patients.

Keywords Superoxide dismutase · Metastatic tumor · Cisplatin–paclitaxel chemotherapy · Nasopharyngeal carcinoma

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2 Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor in the nasopharynx with a high incidence of metastasis. One of the causes is the oxidative reactive oxygen species (ROS) disorder that can disrupt superoxide dismutase (SOD) balance. High levels of ROS cause cell damage and cell death through apoptosis and necrosis [1]. Body has protection against oxidant through SOD which capable of inhibiting DNA chain damage from ROS induction and competing with oxidation reactions, which chemically decreases free radical [2]. Cisplatin–paclitaxel chemotherapy is one of the modalities in the treatment of head and neck malignant tumors [3]. Chemotherapy works by inducing high ROS causing NPC cell death characterized by a therapeutic response of tumor volume reduced [4].

SOD serum levels measurements in NPC patients showed a lower average compared to normal people and this difference was significant ($p = 0.01$). This might be due to the strong tendency of DNA damage or malignant progression that caused decreased antioxidant levels due to continuous resistance through ROS [5]. Hydrogen peroxide (H_2O_2) levels, which increased 1.6 times in NPC patients compared to normal people, showed decreased SOD levels 1.6 times. Malonaldehyde (MDA) as a marker of ROS in NPC patients increased 3.18 times compared to normal people [1].

Cisplatin is a platinum-containing chemotherapy agent that can react in vivo and cause cross-linking of DNA chain, which in turn triggers apoptosis by promoting high production of ROS. Reduction of free radical levels is one of the mechanisms in which antioxidants indirectly affect chemotherapy [1]. Paclitaxel has known having anti-cancer effects since the 1960s. This medicine is derived from Pacific pine bark extract (*Taxus brevifolia*). These pine

seeds contain poisonous alkaloids called taxanes. The results of National Cancer Institute in 1979 concluded that paclitaxel had a role in affecting and damaging cell structure called microtubule [6]. Paclitaxel activates ROS then ultimately activate caspase cascade [7].

The basic pathophysiology of SOD that affects the response of neck tumor metastasis has been studied recently. Body develops a protective mechanism to overcome hazard from free radicals, such as endogenous antioxidants composed of enzymes and synthesized compounds of the body [1]. Enzymes such as catalase, glutathione peroxidase (GSH), SOD are endogenous antioxidants that can be found in various body tissues. Superoxide dismutase is an enzyme that catalyzes the radical superoxide dismutase ions (O_2^-) into hydrogen peroxide (H_2O_2) and oxygen (O_2). Superoxide dismutase plays an important role as an endogenous antioxidant and classified as a primary antioxidant that plays a role in reducing the formation of new free radicals by breaking the chain reaction and changing it into a more stable product [8].

Based the explanation above, this study aimed to know the correlation between SOD serum level alteration with neck tumor metastasis post-chemotherapy of cisplatin–paclitaxel response in nasopharyngeal carcinoma patients at Dr. Soetomo General Hospital Surabaya.

Methods

We took samples from new NPC patients record in ENT unit of Dr. Soetomo General Hospital Surabaya. The inclusion criteria included: A new N1, N2 and N3 NPC patients with all type histopathologies according to WHO. Exclusion criteria were: (1) suffering chronic inflammatory disease (rheumatoid arthritis, referencing phase of ischemic myocardium), (2) receiving injection therapy and oral SOD. The dropout (DO) criteria included very severe ESOs therefore chemotherapy regimens were replaced without cisplatin–paclitaxel, the patient did not come on schedule for chemotherapy for more than 3 weeks, and the patient did not continue chemotherapy or died.

This was a cohort study using pre-post test design without comparison. The study conducted at Oncology Unit and Inpatient Installation, Lotus Room, Otolaryngology Department Dr. Soetomo General Hospital Surabaya. The sample size was 30 respondents. We recorded the characteristic data including: age, sex, ethnicity and occupation. SOD serum levels before and after cisplatin–paclitaxel chemotherapy were assessed by Clinical Pathology Consultant. The data were collected and processed statistically using Wilcoxon Signed Rank Test and

Table 1 Age distribution

Age (years)	N	%
≤ 30	3	10.00
30–39	3	10.00
40–49	8	26.67
50–59	7	23.33
≥ 60	9	30.00
Total	30	100.00

Table 2 Sex distribution

Sex	N	%
Male	19	63.33
Female	11	36.67
Total	30	100.00

Spearman rho correlation test with Statistical Package for Social Sciences (SPSS) program for windows.

Results

From total 30 patients, we found age group of ≥ 60 years was 9 patients (30.00%), 40–49 years was 8 patients (26.67%) and 50–59 years was 7 patients (23.33%). The youngest was 27 years old and the oldest was 70 years old (Table 1). There were 19 male patients (63.33%) and 11 female patients (36.67%). The comparison between men and women was 2:1 (Table 2). The most NPC patients were Javanese as many as 24 patients (80.00%), Madurese 4 patients (13.34%) and Lombok and Sumbawa, 1 patient each (3.33%) (Table 3). The highest occupations were self-employed, 10 patients (33.33%), followed by farmers, 5 patients (16.68%) (Table 4). SOD serum examination before cisplatin–paclitaxel chemotherapy was 179.53 (standard deviation 263.11). We obtained SOD serum examination after cisplatin–paclitaxel 3 series chemotherapy average was 209.13 (standard deviation of 220.27) (Table 4).

Neck tumor metastasis volume (TMV) after 3 series of cisplatin–paclitaxel chemotherapy obtained an average of 62.73 (standard deviation of 147.17) (Table 5). Statistical test using Wilcoxon Sign Rank Test obtained correlation coefficient value $p = 0.000$. This meant that there was a significant change in TMV before and after cisplatin–paclitaxel chemotherapy ($p < 0.05$). SOD level changes before and after cisplatin–paclitaxel chemotherapy obtained Δ average of 29.6 (Δ standard deviation of -42.84). Changes in neck metastasis tumor response (TMV) before and after cisplatin–paclitaxel chemotherapy obtained Δ average of -4.57 and Δ standard deviation of

Table 3 Ethnic distribution

Ethnic	N	%
Javanese	24	80.00
Lombok	1	3.33
Madurese	4	13.34
Sumbawa	1	3.33
Total	30	100.00

Table 4 Occupation distribution

Occupation	N	%
Teacher	4	13.33
Farmer	5	16.68
Self-employee	10	33.33
Pension	1	3.33
Unemployed	10	33.33
Total	30	100.00

Table 5 Superoxide dismutase levels changes and neck tumor metastasis volume (TMV) between pre- and post-cisplatin–paclitaxel chemotherapy

Cisplatin–paclitaxel chemotherapy	SOD serum level (ng/ml)	Neck tumot metastasis (TMV) (cm ³)
Pre-		
Average	179.53	127.3
Median	73	60.5
Standard deviation	263.11	208.59
Post-		
Average	209.13	62.73
Median	108	4
Standard deviation	220.27	147.17
Δ (delta)		
Average	29.6	– 64.57
Median	35	– 56.5
Standard deviation	– 42.84	– 61.42

– 61.42. Statistical test using Spearman rho obtained correlation coefficient (r) of 0.180 and p value = 0.340. There was non-significant correlation between SOD serum level alteration with neck tumor metastatic post-cisplatin–paclitaxel response chemotherapy in NPC patients with $p > 0.05$.

Discussion

SOD serum levels after cisplatin–paclitaxel chemotherapy were obtained an average of 209.13, median of 108, standard deviation of 220.27. There was an increase in SOD

levels average after cisplatin–paclitaxel chemotherapy. This did not correspond to the ROS mechanism that caused a decrease in SOD serum levels. Measurement of SOD serum levels in NPC patients showed a lower average compared to normal people and this difference was significant ($p = 0.01$) [5].

Several studies reported low antioxidant serum levels in cancer patients, as well as a decrease in SOD levels in blood and tissue in head and neck cancer patients. Cisplatin is a platinum-containing chemotherapy agent that can react in vivo and cause cross-linking in the DNA chain that eventually leads to apoptosis [9]. Paclitaxel activates ROS which in turn also activates caspase cascade [6]. DNA damage or malignant progression leads to a decrease in SOD levels because of continuous resistance to ROS [5]. The effects of necrosis and apoptosis of NPC cells after chemotherapy will lead to a decrease in proliferation with clinical manifestations in the form of reduced malignancy progress. The reduced malignant progression, SOD levels increases [10].

Other studies measured MDA, SOD, CAT and GSH of blood before and after chemotherapy in 24 patients with malignant head and neck tumors compared to 17 healthy people as control group. Results obtained 24 patients with higher MDA levels than the control group, while SOD and CAT levels were lower. There was no statistically significant difference of GSH levels in both groups, indicating that MDA levels were higher in patients compared with control group. After chemotherapy, MDA levels were higher, while SOD levels gradually increased [11].

The average of neck TMV before cisplatin–paclitaxel chemotherapy was 127.3, median was 60.5 (standard deviation 208.59). The result of TMV measurement after cisplatin–paclitaxel chemotherapy was obtained average of 62.73, median of 4, standard deviation of 147.17. There was a decreased average of TMV after cisplatin–paclitaxel chemotherapy. This corresponded to the use of cisplatin–paclitaxel chemotherapy in the management of malignant tumors that was to eradicate tumor cells or to control locoregional when it was used together with surgery or radiotherapy [12]. Chemotherapy is used to treat macroscopic and microscopic metastases. Microscopic metastases that are clinically invisible and deposited in the body, if not treated then will be macroscopic [13].

Statistical test of SOD serum level alteration with neck tumor metastatic post cisplatin–paclitaxel response chemotherapy was $r = 0.180$ and $p = 0.340$. The results showed a non-significant relationship ($p > 0.05$). Cisplatin–paclitaxel has mechanism of inducing ROS as a result of its active metabolite. Moreover, besides chemotherapy agents, the tumor regression itself was thought to alter the free radical [10].

In this study SOD levels alteration might be due to direct effects of chemotherapy or indirect effects of tumor regression. The direct effect was that cisplatin–paclitaxel chemotherapy induced ROS either in the form of free radicals, reactive anions containing oxygen atoms or molecules containing oxygen atoms that could produce free radicals, or chemically activated by them. Those examples were hydroxyl radicals, superoxide, hydrogen peroxide, and peroxynitrite. The high ROS would directly affect SOD levels that become front-line defense against free radicals. Indirect effects was that the occurrence of necrosis and apoptosis in NPC cell post-chemotherapy caused remission and gave the body a chance to rebalance SOD levels [10].

We suggested that there was another path than ROS pathway that caused apoptosis that was extrinsic pathways that caused apoptosis going on despite SOD levels increased. The extrinsic pathway involved the activation of tumor necrosis factor receptors (TNF). Such as Fas receptor activation by Fas ligand. Activation and trimerization of receptor would carry the procaspase-8 molecule and cause autocatalysis and then activate the 8-caspase molecule. Activation of caspase-8 would activate other caspase effects. Such as caspase-3 might cause apoptosis or activate Bid that would interact with Bcl-2 to initiate intrinsic pathway [14]. Tumor necrosis factor would increase p53 protein in addition to suppressing CDK activity also triggering an increase in BAX protein activity. The BAX protein suppressed Bcl-2 activity in the mitochondrial membrane, resulting a decrease of Bcl-2 function then resulting in Cytochrome-C release to the cytosol. Cytochrome-C then activated Apaf-1. Furthermore Apaf-1 activated caspase cascade and apoptosis [15].

Conclusion

There was no correlation between superoxide dismutase level alteration with neck tumor metastatic post cisplatin–paclitaxel chemotherapy in patients with nasopharyngeal carcinoma. We suggest a further research is needed to involve other variables such as TNF- α and p53 and a CT-scan is required to calculate TMV by measuring the length, width and height of the tumor close to its original volume.

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