Indonesian Journal of Cancer Chemoprevention, June 2023
ISSN: 2088–0197
e-ISSN: 2355-8989

Effect of Astaxanthin Supplementation in Preventing Anemia in Head and Neck Cancer Patients Receiving Cisplatin Chemotherapy

Yusuf Aminullah[1*], Hertanto Wahyu Subagio[2], Damai Santosa[3], Zulfikar Naftali[4]

[1]Doctor of Medicine and Health Study Program, Faculty of Medicine, Universitas Diponegoro/RSUP Dr. Kariadi Semarang
[2]Nutrition Study Program, Faculty of Medicine, Universitas Diponegoro/RSUP Dr. Kariadi Semarang
[3]Internal Medical Study Program, Faculty of Medicine, Universitas Diponegoro/RSUP Dr. Kariadi Semarang
[4]Otolaryngology Study Program, Faculty of Medicine, Universitas Diponegoro/RSUP Dr. Kariadi Semarang

Abstract

The incidence of anemia due to reactive oxygen species (ROS) in patients with head and neck cancer (HNC) can be caused by a side effect of cisplatin chemotherapy, namely myelosuppression. In the presence of ROS, external antioxidants are needed, including astaxanthin as an antioxidant to neutralize and fight ROS in preventing anemia. This study aims to prove and analyze the antioxidant effect of astaxanthin in preventing anemia in HNC patients due to cisplatin chemotherapy for 3 weeks. The study design was a randomized controlled trial pre-post test design, involving 42 research subjects who were randomly divided into two groups, then 3 cc of blood was taken I to check the hemoglobin level and the number of erythrocytes. The treatment group was given astaxanthin 2x4 mg and the control group was given a combination of vitamin C 1x500 mg and vitamin E 1x250 IU for 3 weeks then 3 cc of blood was taken II to check hemoglobin levels and erythrocyte counts. The independent variable is intake of astaxanthin, the dependent variable is hemoglobin level and the number of erythrocytes and the confounding variables are age, sex, type of HNC, stage of HNC, ECOG and BMI. Data analysis was performed by the Descriptive test, Levene test, Shapiro Wilks, Wilcoxon test, and Mann-Whitney test. The significance of the hypothesis test was obtained with $p<0.05$. The 42 research subjects met the inclusion criteria, most aged between 41-50 years, male and female ratio 2:1, The most HNC were Nasopharyngeal Cancer, the most HNC stage was stage IV, the most HNC performance status was ECOG I and the most HNC patients had normal BMI. There was a significant difference in hemoglobin levels $p=0.012$ ($p<0.05$) and the number of erythrocytes, $p=0.04$ ($p<0.05$) between the treatment and control groups. There was a significant difference in hemoglobin levels after therapy in the treatment and control groups $p=0.012$ ($p<0.05$) and the number of erythrocytes $p=0.04$ ($p<0.05$) between the treatment and control groups. Astaxanthin can prevent anemia in the form of decreased hemoglobin levels and the number of erythrocytes in HNC patients who receive cisplatin chemotherapy.

Keywords: *astaxanthin, anemia, HNC, cisplatin, ROS.*

Submitted: April 09, 2023
Revised: May 26, 2023
Accepted: May 30, 2023
Published online: June 22, 2023

*Corresponding author: yusufaminullah75@gmail.com

INTRODUCTION

Head and neck cancer (HNC) is a variety of malignant tumors originating in the upper aerodigestive tract which includes the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, paranasal sinuses as well as salivary glands (Mehanna, 2010; Mateos, 2016; Franzman, 2010).

The incidence of HNC ranks in the top six, which is about 4% of all cancers in the world. The World Health Organization (WHO) in 2006 stated that there were 600,000 new cases of HNC with 300,000 deaths each year worldwide. In the United States, the incidence of HNC is about 3-5% of all cancers, often occurring in men older than 50 years. According to the Indonesian Cancer Registration Agency, HNC ranks fourth out of the top ten cancers in men and women and second out of the top ten cancers in men. The incidence of HNC at Dr. Kariadi Hospital Semarang during March-April 2015 was 36 cases, with the most diagnoses being nasopharyngeal cancer, followed sinonasal cancer and laryngeal cancer. This study also showed the average age of HNC patients was 50 years, the youngest age was 14 years and the oldest was 67 years. Characteristics of HNC sufferers according to sex, men 21 (58.3%) more than women 15 (41.7%) or 3:2 (Soekamto, 2002; Ramdhani, 2015).

Management of HNC includes surgery, radiation, chemotherapy, and a combination depending on the stage of cancer and the type of its histopathology. Histopathologically, squamous cell carcinoma reaches 95% of all HNC cancers in addition to lymphoma, sarcoma, adenocarcinoma, basal cell carcinoma, and melanoma (Brockstein dan Vokes, 2006).

Chemotherapy works systemically and non-selectively so that it has side effects, namely not only cancer cells that experience apoptosis but healthy cells throughout the body are also affected as a result of the formation of free radical compounds. This compound is toxic in the body when the amount is excessive, so it can damage normal cells in the body including bone marrow cells resulting in a decrease in the hemopoietic system characterized by one of the signs of anemia on routine blood tests (Johnson and O'Dwyer, 2005; Munir, 2007; Vokes and Chong, 2008).

Lee, *et al.* (2005) examined the effect of cisplatin chemotherapy on bone marrow in 274 gynecologic cancer patients and 503 breast cancer patients. The decline in the hemopoietic system began to occur at the beginning of the chemotherapy series and tended to increase at the end of the chemotherapy series, which was 28.8% of patients.

Baron, *et al.* (2016) researched a decrease in hemoglobin, leukocyte, and platelet values due to the formation of free radicals. Arfiputri, *et al.* (2017) proved that 4 times cisplatin chemotherapy in stage III B cervical cancer patients caused bone marrow depression in the process of hematopoiesis, especially a decrease in erythrocytes, leukocytes, and platelets. Zulkarnaen, *et al.* (2017) showed a decrease in hemoglobin, neutrophils, and platelets after cisplatin-paclitaxel chemotherapy in patients with head and neck malignant tumors.

A decrease in the number of hemopoietic cells will also reduce hemoglobin levels and the number of erythrocytes characterized by anemia so that it will affect the general condition of the patient, reduce oxygen levels distributed to body cells and worsen the prognosis, (Soebandiri, 2014). In addition, if anemia occurs, the next series of chemotherapy in HNC patients will be delayed so that cancer therapy cannot be carried out effectively and prolong the length of stay (LOS) of HNC patients.

Anemia is a condition in which the number of erythrocytes and/or hemoglobin levels in the blood is reduced so that it cannot carry out its function of carrying sufficient O_2 to the tissues. Anemia in HNC patients is caused by the presence of free radicals due to the side effects

of cisplatin chemotherapy which causes the eradication process of cancer cells to run ineffectively. In addition, anemia in HNC patients can cause a decrease in quality of life and increase mortality by up to 65%. In patients with carcinoma of the brain and neck, anemia increases the risk of death by 75% while in lymphoma patients it reaches 67% (Rouli and Pustika, 2005).

Based on this, the incidence of anemia in HNC patients is important for prevention so that the quality of life of HNC patients increases, chemotherapy becomes more effective and does not worsen the prognosis by providing antioxidants from outside to fight free radicals that can cause anemia.

Antioxidants from outside are needed because natural antioxidants in the body are not able to fight free radicals from outside the body so antioxidants from outside the body are needed to prevent anemia from damage to body tissues that occur due to free radicals caused by cisplatin chemotherapy by stabilizing free radicals, complementing the lack of electrons owned by free radicals and inhibiting chain reactions due to formation of free radicals that can cause oxidative stress. Some antioxidants are often used such as green tea, vitamin C, vitamin E, lycopene, lutein, selenium, astaxanthin, and others (Purwata, 2016; Sayuti and Yenrina, 2015; Suryohudoyo, 2000; Pavlovic, 2005).

Astaxanthin can stop the free radical chain reaction and inhibit damage to normal cells by binding free radicals and stop the chain of free radicals that affect the bone marrow so that the side effects of anemia can be prevented (Suseela and Toppo, 2006; Nishida, *et al*., 2007; Odeberg, *et al.*, 2003).

Astaxanthin's antioxidant activity is stronger than other antioxidants such as beta carotene, lutein, lycopene, and vitamin E because it has a carotenoid structure that is rich in electrons, not prooxidant, resistant to autooxidation, and has better strength in neutralizing singlet oxygen, digesting free radicals, providing protection again lipid peroxidation and oxidation damage (Suseela and Toppo, 2006; Nishida, *et al*., 2007; Odeberg, *et al*., 2003).

Based on research by Xue, *et al.* (2017) that Astaxanthin as an antioxidant has been tested *in vitro* with the results that Astaxanthin can be used as a potential therapy to protect hemopoietic activity from bone marrow damage due to radiation in rats. In this study, astaxanthin was implemented as an antioxidant in HNC patients receiving cisplatin chemotherapy in preventing decreased hemopoietic activity.

Based on the ability and advantage of astaxanthin antioxidants in inhibiting normal cell death by neutralizing and fighting free radicals and there has been no research that assesses the effect of astaxanthin in preventing anemia in the form of a decrease in hemoglobin levels and erythrocyte counts in HNC patients receiving cisplatin chemotherapy, research was conducted to answer these problems.

The purpose of the study was to prove astaxanthin in preventing anemia in HNC patients due to cisplatin chemotherapy.

MATERIALS AND METHODS

Research Materials

The research materials were 4 mg astaxanthin supplement given twice a day to the treatment group and 500 mg vitamin C and 250 IU vitamin E supplements given once a day.

Research Methods

Design, Time, and Place

The rearch design is the Experimental Randomized Controlled Clinical Trial Pre and Post Test Design which was carried out in the Cassowary Installation Room of Dr. Kariadi Hospital Semarang from June to December 2022.

Table 1. Description characteristics of the study samples in the treatment and control group.

Variable	Treatment (%) n=21	Control (%) n=21	*p*
Age (years)			0.536
11-20	-	1 (4.8)	
21-30	3 (14.3)	-	
31-40	4 (19)	3 (14.3)	
41-50	8 (38)	8 (38)	
51-60	3 (14.3	4 (19)	
61-70	2 (9.6)	5 (23,9)	
71-80	1 (4.8)	-	
Gender			0.182
Man	13 (61.9)	14 (66,7)	
Woman	8 (38.1)	7(33.3)	
Types of HNCs			0.415
Nasopharyngeal carcinoma	12 (57)	10 (47,6)	
Sinonasal carcinoma	4 (19)	4 (19)	
Laryngeal carcinoma	1 (4.8)	2 (9.5)	
Tonsil carcinoma	1 (4.8)	-	
Cavum nasi carcinoma	1 (4.8)	-	
Carcinoma of the tongue	1 (4.8)	1 (4.8)	
Parotid carcinoma	-	1 (4.8)	
NHL colli	1 (4.8)	2 (9.5)	
Pharyngeal adenocarcinoma	-	1 (4.8)	
Stage			0.004
II	-	-	
III	6 (28.6)	4 (19.1)	
IV	15 (71.4)	17 (80.9)	
ECOG			0.859
I	16 (76.2)	15 (71.4)	
II	4 (19)	5 (23.8)	
III	1 (4.8)	1 (4.8)	
BMI			0.657
Underweight (<18.5)	4 (19)	3 (14.3)	
Normal (18.5-22.9)	16 (76.2)	14 (66.7)	
Overweight (23-24.9)	1 (4.8)	2 (9.5)	
Obesity I (25-29.9)	-	2 (9.5)	
Obesity II (>30)	-	-	

Levene Test; p>0.05 (homogen)

Research Subjects

The subjects of the study were HNC patients who underwent cisplatin chemotherapy taken by consecutive sampling, with criteria for inclusion of HNC patients with cisplatin chemotherapy, stadium II-IV, aged >11-<80 years, ECOG I-III, and willing to follow the research stage by signing informed consent. While patients who received radiotherapy, and blood transfusions, consumed other antioxidants, the presence of stomach, liver, and kidney disorders and hematologic malignancies were not included in this study. The drop-out criteria in this study were: the general condition of the patient worsened,

acquired an allergy to astaxanthin or cisplatin, and not complying with the rules of the study. Refusing or do not want to continue research.

The calculation of the minimum sample size using the error rate (α) = 5% power test = 90% standard deviation from the study, so that the total research subjects needed are as many as 42 people. The research has been approved by the Medical Research Ethics Commission of the Faculty of Medicine UNDIP/Dr. Kariadi Hospital Semarang Number. 1066/EC/KEPK-RSDK/2022.

Data Collection

This study included 42 research subjects, then randomly divided into 2 groups, namely the treatment and control groups, 3 cc of blood was taken I to check hemoglobin levels and erythrocyte counts one day before cisplatin chemotherapy. In the treatment group, astaxanthin was given 2x4 mg per day, while in the control group it was given vitamin C 500 mg per day and vitamin E 250 IU per day after the first blood draw until 1 day before the next series of cisplatin chemotherapy (for 3 weeks).

Table 2. Homogeneity test of hemoglobin and erythrocyte levels before therapy in the treatment and control group.

	Treatment group (n=21)	Control group (n=21)	
	Mean	Mean	*p*
Hemoglobin (g%)	11.7 (1.44)	10.8 (0.89)	0100
Erythrocytes (million/mm^3)	4.1 (0.76)	3.7 (0.37)	0.031
Leucocytes (thousand/mm^3)	6.8 (3.08)	5.6 (3.58)	0.987
Thrombocytes (thousand/mm^3)	289.3 (97.85)	302.3 (141.63)	0.177

Levene Test; p>0,05 (homogen)

After 3 weeks, or 1 day before the next series of cisplatin chemotherapy, the two groups took 3 cc of blood II to check hemoglobin levels and the number of erythrocytes according to the study protocol.

Hemoglobin levels and erythrocyte counts in research subjects were obtained from the results of examination using the Hematology Analyzer method, using the Sysmex XN 1000 Hematology Analyzer tool. Descriptive data include demographic data (age, sex), type of HNC, stage of HNC, ECOG, and BMI.

Data Processing and Analysis

Data were analyzed using the Descriptive test to determine the description of the characteristics of the study sample, the Levene test to determine the homogeneity of the hemoglobin level and the number of erythrocytes before the study, the Shapiro Wilks test to determine the normality of the hemoglobin level and the number of erythrocytes before the study, the Wilcoxon test to determine the average hemoglobin level and the number of erythrocytes

Table 3 Normality test of hemoglobin levels and erythrocyte counts before therapy in the treatment and control group.

	Treatment group (n=21)		Control group (n=21)	
	Mean	*p*	Mean	*p*
Hemoglobin (g%)	11.7 (1.44)	0.998	10.8 (0.89)	0.792
Erythrocytes (million/mm^3)	4.1 (0.76)	0.253	3.7 (0.37)	0.975
Leucocytes (thousand/mm^3)	6.8 (3.08)	0.006	5 .6 (3.58)	0.000
Thrombocytes (thousand/mm^3)	289.3 (97.85)	0.011	302.3 (141.63)	0.013

Saphiro Wilk; p>0.05 (Normal distribution)

Table 4. Average hemoglobin levels and erythrocyte counts before and after therapy in the treatment and control group.

	Mean before therapy	Mean after therapy	*p*
Treatment Group (n=21)			
Hemoglobin (g%)	11.7 (1.44)	11.2 (1.21)	0.085
Erythrocytes (million/mm³)	4.1 (0.76)	3.9 (0.54)	0.048
Leucocytes (thousand/mm³)	6.8 (3.08)	5.8 (2.77)	0.122
Thrombocytes (thousand/mm³)	289.3 (97.85)	298.7 (132.2)	0.664
Control Group (n=21)			
Hemoglobin (g%)	10.8 (0.89)	10.3 (1.17)	0.014
Erythrocytes (million/mm³)	3.7 (0.37)	3.4 (0.37) 0	.002
Leucocytes (thousand/mm³)	5.6 (3.58)	3.8 (1.59)	0.003
Thrombocytes (thousand/mm³)	302.3 (141.6)	253.1 (122.63)	0.039

Wilcoxon test; p<0.05 (significant)

before and after therapy (paired test), as well as the Mann Whitney test to determine the average hemoglobin level and erythrocyte count after therapy (different test). The significance of the hypothesis test was obtained through a non-parametric test with $p<0.05$. Data were analyzed with SPSS (Statistical Package for the Social Sciences) 25.0.

RESULTS

Characteristics of Research Subjects Result

Forty-two research subjects met the inclusion criteria, most aged 41-50 as many as 16 people (38.1%) years, male and female 2:1, Naopharyngeal cancer 22 people (52.4%), stage IV 32 people (76 .2%), ECOG I 31 people (73.8%) and Normal BMI 30 people (71.4%) (Table 1).

Three patients dropped out of the study, namely 1 subject in the treatment group and 2 subjects in the control group. Two subjects in the control group because their general condition worsened after cisplatin chemotherapy, while 1 subject in the treatment group dropped out because they didn't drink astaxanthin regularly.

The patient's adherence to taking astaxanthin in the treatment group and taking vitamin C 500 mg and E 250 IU in the control group was evaluated by the researchers by asking the remaining astaxanthin, vitamins C and E that had been taken during the control and asking whether there were other antioxidants consumed by the patient during the treatment group. during control at the clinic.

Data Homogeneity and Normality Test

The results of the homogeneity test of hemoglobin levels and the number of erythrocytes before therapy in the treatment and control group with the Levene test showed homogeneous results where hemoglobin levels were $p=0.1000$ ($p>0.05$), while the number of erythrocytes was inhomogeneous where $p=0.031$ ($p<0.05$) (Table 2).

The results of the normality test with hemoglobin levels and erythrocyte count before therapy showed hemoglobin levels of the treatment group $p=0.998$ ($p>0.05$) and the control group, $p=0.792$ ($p>0.05$), while the number of erythrocytes before therapy in the treatment group was $p=0.253$ ($p>0.05$) and the control group $p=0.975$ ($p>0.05$) (Table 3).

Hemoglobin levels and erythrocyte count before therapy in treatment and control group were normally distributed. Based on the results of homogeneity and normality tests, the data were analyzed by non-parametric tests.

There was a not significant decrease in hemoglobin levels before and after therapy in the treatment group p=0.085 (p>0.005), while in the control group, there was a significant decrease p=0.048 (p<0.05). There was a significant decrease in the number of erythrocytes before and after therapy in the treatment group p=0.014 (p<0.05) and the control group p= 0.002 (p<0.05) (Table 4).

There was a significant difference in the decrease in hemoglobin levels p=0.012 (p<0.05) and erythrocyte count p=0.004 (p<0.05) between the treatment and control groups (Table 5).

DISCUSSION

Characteristics of Research Subject

In this study, age, gender, type of HNC, ECOG and BMI did not affect the decrease in hemoglobin levels and the number of erythrocytes, while the stage of the HNC did affect the decrease in the level of hemoglobin and the number of erythrocytes. These results indicate that the higher the HNC stage, the higher the decrease in hemoglobin levels and the number of erythrocytes which will result in anemia due to a decrease in the number of hemopoietic cells which will affect the general condition of the patient, reduce the level of oxygen distributed to the body's cells and worsen the prognosis (Soebandiri, 2014).

The mean age of the study sample was 48.2 years, the youngest was 18 years and the oldest was 77 years. These results are in accordance with research at Dr. Kariadi Semarang in March-April 2015 where the most number of HNCs were in the age group over 40 years and the incidence increased with age (Ramdhani, 2015), The incidence of HNCs in the United States often occurs in men over 50 years of age (National Cancer Institute, 2006).

The causes of HNC are multifactorial, exposure to carcinogenic substances, and infection with the Ebstein-Barr virus can cause the accumulation of gene abnormalities that result in the transfomation towards cancer cells. This process takes decades so the frequency of HNCs increases with age (Franzmann, 2006).

The characteristics of the sample by sex were that male patients numbered more, 27 (64.3%), compared to female patients, 15 (35.7%), with a ratio of 2:1. This result is in accordance with Munir's research at Dr. Cipto Mangunkusumo Hospital Jakarta where the prevalence of men is greater than women to be affected by HNC (Munir, 2007). This result is similar to the incident in the United States where only one-third of HNC sufferers are female (National Cancer Institute, 2006). Inside the Dr. Kariadi Hospital Semarang in March-April 2015, HNC cases were found more in men with a ratio of men and women 2:1. This causes the number of male sufferers to suffer more from nasopharyngeal carcinoma because it is thought to be due to habits related to carcinogenic materials (smoking, drinking alcohol) and the work environment that has great potential exposure to carcinogenic materials (Franzmann, 2006).

The distribution of HNC types showed that the largest type of malignancy was nasopharyngeal carcinoma, with 22 (52.4%) cases,

Table 5. Average hemoglobin level and number of rrythrocytes after therapy in treatment and control groups.

	Mean treatment group (n=21)	Mean control group (n-21)	*p*
Hemoglobin (g%)	11.2 (1.21)	10.3 (1.17)	0.012
Erythrocytes (million/mm3)	3.9 (0.54)	3.4 (0.37)	0.004
Leucocytes (thousand/mm^3)	0.2 (2.77)	3.8 (1.59)	0.009
Thrombocytes (thousand/mm^3)	98.7 (132.2)	253.1 (122.63)	0.178

Mann Whitney test; p<0.05 (significant)

which was the most common malignancy in the head and neck area. The incidence of HNC at Dr. Kariadi Hospital was 448 cases, with the highest percentage being nasopharyngeal cancer (60%) followed by nose and paranasal sinus cancer (18%), laryngeal cancer (16%) and cancer of the oral cavity, tonsils and hypopharynx with a low percentage (Ramdhani, 2015).

The stage of HNC in this study was generally advanced, namely stadium IV as many as 32 (76.2%) samples, and stage III as many as 10 (23.8%) samples. Patients come for treatment usually when it is at an advanced stage where the tumor has expanded to the surrounding tissue or lymph glands of the neck and greatly interferes with daily activities. This is due to the lack of public knowledge about HNC, especially early symptoms. Besides that, low socioeconomic conditions cause patients to come late for treatment, and in the early stages of the disease, HNC has not given complaints that disturb daily life so that it is less noticed by sufferers.

ECOG in this study is generally ECOG 1, which is 31 (73.8%) samples, ECOG II as many as 9 (21.4%) samples, and ECOG III as many as 2 (4.8%). HNC patients come for treatment mostly in ECOG 1 (good) conditions. This is due to the incvreasing performance status of people with a culture of healthy living.

The BMI of patients in this study was generally normal (18.5-22.9), namely 30 (71.4%) samples, underweight (<18.5) as many as 7 (16.7%) samples, overweight (23-24.9) as much as 3 (7.1%) and obesity I (25- 29.9) as much as 2 (4.8%). HNC patients who seek treatment on average have a normal BMI, where patients have a balance of body weight and height. This is due to the increasing public knowledge about healthy and good food nutrition intake in daily lifestyle, in addition to the increasing socioeconomic condition of the community.

There are differences in the sensitivity of each individual to a decrease in hemoglobin levels and erythrocyte counts, even in some patients who can experience a decrease in hemoglobin levels and erythrocyte counts after the first administration of cisplatin. The cause of differences in sensitivity to this drug is due to differences in drug pharmacokinetics in the body and drug absorption power by patients. (Barabas, 2008 dan Ekborn, 2003).

There is a correlation between patients undergoing cisplatin chemotherapy with decreased hemoglobin levels and erythrocyte counts in the form of anemia, This is because cisplatin can cause an increase in the production of reactive oxygen species (ROS) in the body. The accumulation of ROS will release cytochrome-c from mitochondria through the activation of c-Jun-N-terminal kinase (JNK) and p38MAPK. Cytochrome-c will then activate caspase-8, -9, and -3 (intrinsic pathway apoptosis), causing cell apoptosis, in this case haemopoetic cells, resulting in a decrease in hemoglobin levels and the number of erythrocytes resulting in anemia (Barabas, 2008 and Ekborn, 2003).

The decrease in hemoglobin levels and the number of erythrocytes due to cisplatin is also related to the dose given. Administration of cisplatin at the repetition of therapy for the next series will increase the cumulative effect of cisplatin (Barabas, 2008 and Ekborn, 2003).

Lee, *et al.* (2005) examined the effect of cisplatin chemotherapy on bone marrow in 274 gynecologic cancer patients and 503 breast cancer patients. The result was 28.8% decreased hemopoietic system began to occur in series I as much as 34.7%, series II as much as 63.4%, and series III as much as 75.7% p there were patients with gynecological cancer, while in breast cancer, patients began to experience a decrease in the hemopoietic system at series I as much as 26.2%, series II as much as 53% and series III as much as 72.1%.

Astaxanthin can prevent a decrease in hemoglobin levels and the number of erythrocytes in HNC patients receiving cisplatin

chemotherapy. This is because cisplatin works systemically so that it can affect the bone marrow throughout the body, as a result of which precursor cells and differentiation cells in the bone marrow, as well as mature cells in the blood circulation, will be affected by cisplatin administration. Hemopoietic system cells including hemoglobin and erythrocytes will be damaged, mitosis decreases and apoptosis occurs so that it can result in decreased hemoglobin levels and erythrocyte counts resulting in anemia (Mazza, 2002; Ramnik, 2003; Ronald and Richard, 2004).

Anemia occurs due to a decrease in hemoglobin levels and erythrocyte count due to changes in the hemopoietic system, namely the death of blood embryonic cells after exposure to cisplatin chemotherapy because exposure to cisplatin causes free radicals that cause bone marrow depression (myelosuppression) (Mazza, 2002; Ramnik, 2003; Ronald and Richard, 2004).

The decrease in hemoglobin levels and the number of erythrocytes was lower in the treatment group than in the control group and showed significant differences. This is due to a decrease in hemoglobin levels in line with a decrease in erythrocytes, depending on the polypeptide chain attached to the heme between erythrocytes and oxygen bound to hemoglobin in the form of oxyhemoglobin (Mazza, 2002; Ramnik, 2003; Ronald and Richard, 2004).

Astaxanthin as an antioxidant from the outside will bind free radicals that affect the bone marrow so that it can inhibit the decrease in hemoglobin levels and erythrocyte count. Astaxanthin is more powerful than other antioxidants such as vitamins C and E because it has a carotenoid structure which is rich in electrons, is not a pro-oxidant like vitamins C and E, is resistant to auto-oxidation and has better power in neutralizing singlet oxygen, digesting free radicals, providing protection against Lipid peroxidation and oxidative damage (Suseela and Toppo, 2006; Nishida, *et al.*, 2007; Odeberg, *et al.*, 2003).

In this study, it can be considered the administration of astaxanthin to prevent a decrease in hemoglobin levels and erythrocyte count in the administration of cisplatin chemotherapy to prevent delays in the next series of cisplatin chemotherapy due to a decrease in the patient's general condition and improve the prognosis of HNC patients.

The effect of astaxanthin in the form of gastrointestinal disorders (nausea and heartburn) was found in 3 patients in the treatment group (Table 5). These side effects have been resolved by administering 3x1 antacid tablets and patients can continue the study again.

Patient adherence to taking drugs and consumption of other antioxidants was controlled by researchers by asking about the remaining drugs that had been taken at the time of control and asking whether there were other antioxidants consumed by patients at the time of control to the ENT clinic.

Three patients dropped out of the study, namely 2 samples of the control group because the general condition worsened after cisplatin chemotherapy, while one sample of the treatment group refused to continue the study.

Research Limitations

The results of this study cannot explain all problems, due to the limitations of the study, among others: the possibility of research subjects consuming drugs or foods containing other antioxidants, differences in the nutritional status of sufferers, and differences in the ability and absorption power of food and drugs. These factors have been tried to be resolved by explanation to patients every time before the administration of astaxanthin.

CONCLUSION

Cisplatin chemotherapy given to HNC patients can cause anemia in the form of decreased hemoglobin levels and the number of erythrocytes due to myelosuppression due to free

radicals produced by cisplatin. Astaxanthin as an external antioxidant can prevent anemia by preventing a decrease in hemoglobin levels and the number of erythrocytes in MPA patients receiving cisplatin chemotherapy.

Referring to the results of this study, it is necessary to conduct further research on the provision of other antioxidants in HNC patients in preventing anemia due to the emergence of free radicals due to cisplatin chemotherapy.

ACKNOWLEDGEMENT

Thanks to God, my family, supervising teachers, Kasuari Installation of RSUP Dr. Kariadi Semarang and other parties who have assisted in this research.

REFERENCES

Arfiputri, V.F., 2017, *Perbedaan kadar hemoglobin, eritrosit, leukosit, dan trombosit sebelum dan sesudah kemoterapi cisplatin pada pasien kanker serviks stadium III B di poli onkologi satu atap RSUD dr. Soetomo Surabaya*, *Thesis*, Universitas Airlangga, Surabaya.

Barabas, K., Milner, R., Lurie, D., and Adin, C., 2008, Cisplatin: a review of toxicities and therapeutic applications, *Vet & Comp Oncol*, **6**(1), 1-18.

Baron, R.E., Julve, J.V., Jaime, S.P., Santalo, N.B., Millan, C.V., and Mata, M.L., 2005, Haemoglobin levels and acute radiotherapy induced toxicity, *Tumori*, **91**(1), 40–45.

Barrett-Lee, P., Bokemeyer, C., Gascon, P., Nortier, J.W.R., Schneider, M., Schrijvers, D., *et al*., 2005, Management of cancer-related anemia in patients with breast or gynecologic cancer: New insights based on results from the european cancer anemia survey, *Oncologist*, **10**(9), 743–757.

Brockstein, B.E., and Vokes, E.E., 2006, Principles of chemotherapy in the Management of Head and Neck Cancer, In: Bailey, B.J., Calhoun, K.H., editors, *Head and neck surgery-otolaryngology.* 4ed. Lippincot, William & Wilkins, Philadelphia.

Ekborn, A., 2003, *Cisplatin induce ototoxicity, pharmacokinetics, prediction and prevention, Dissertation*, Department of Otolaryngology and Head & Neck Surgery Karolinska Hospital, Stockholm.

Franzmann, E., Lilly, S., Huang, D., and Thomas, G., 2006, Oncology of head and neck tumors. In: Van De Water, T.R., Staecker, H. editors, *Otolaryngology basic science and clinical review, New York: Thieme. pp. 159-171.*

Franzmann, E.L., Huang, D., and Thomas, G., 2010, Head and neck cancer: changing epidemiology and public health implications. Review article head and neck cancer. *Journal of Oncology*.

Hasselt, C.A., 1998, Nasopharyngeal carcinoma, in: Andrew, S.J., David, E.P. editors, *Disease of the Head and Neck, Nose and Throat, London: Arnold. pp. 297-307.*

Johnson, S., and O'Dwyer, P., Cisplatin and its analogues. In: DeVita V, Hellman S, Rosenberg S, editors, 2005, *Cancer Principles and Practice of Oncology, 7th ed., Philadelphia: Lippincott, pp. 344-54.*

Mateos, J.F., Tamayo, R.S., Mesia, R., Taberna, M., Borgonon, M.P., Ruiz, E.P., *et al*., 2016, Epidermal growth factor receptor (EGFR) pathway polymorphisms as predictive markers of Cetuximab toxicity in locally advanced head and neck squamous cell carcinoma (HNSCC) in a Spanish population, *Oral Oncology,* **63**, 38–43.

Mazza, J.J. (2002). Hematopoiesis and hematopoietic growth factors. In. Mazza JJ, editor. Manual of clinical hematology. Lippincott Williams & Wilkins, Philadelphia.

Mehanna, H., West, C.M.L., Nutting, C., and Paleri, V., 2010, Head and neck cancer--Part 2 : Treatment and prognostic factors, *Journal of British Medical*, **341**, c4690.

Munir, M., 2007, Keganasan di bidang telinga hidung tenggorok, In: Soepardi, E.A., Iskandar, N., Bashiruddin, J., and Restuti, R.D, 6th ed,

Jakarta, Balai Pustaka FKUI.

National Cancer Institutes, 2006, Head and neck cancer: Available from URL: http://www.cancer.gov/cancerinfo/type s/head-and-neck.

National Library of Medicine. Medline Plus. (2006). Head and neck cancer. Available from URL: www.nlm.nih.gov/medlineplus/headandneckcancer.html.

Nishida, Y., Yamashita, E., and Miki, W, 2007, Quenching activities of common hydophilic and lipophilic antioxidants againts singlet oxygen using chemiluminescence detection system, *Carotenoid Science*, **11**, 16-20.

Odeberg, J.M., Lignell, A., Pettersson, A., and Hoglund, P., 2003, Oral bioavailability of the antioxidant astaxanthin in human is enhanced by incorporation of lipid based formulations, *Journal European of Pharmaceutical Sciences*, **19**(4), 299-304.

Pavlovic, V., Cekic, S., Rankovic, G., and Nenad, S., 2005, Antioxidant and pro-oxidant effect of ascocbic acid, *Act Med Median*, **44**(1), 65–69.

Purwata, M., 2016, Antioksidan, Ilmu Kedokteran Molekul, Bali: CV. Infomedika.

Ramdhani, A., 2015, Karakteristik pasien keganasan kepala dan leher yang mendapatkan kemoterapi di RSUP Dr. Kariadi Semarang periode Maret-April 2015.

Sood, R., 2003, *Haematology for students and practitioners*, 5th ed, New Delhi: Jaypee Brotrhers.

Ronald, A.S., Richard, A.M., 2004, Alih bahasa: Brahm, U., Pendit, and Wulandari, D. editor: Hartanto, H., *Tinjauan klinis hasil pemeriksaan laboratorium, 11th ed, Jakarta: EGC*.

Rouli, N., and Amalia, P., 2005, Anemia pada penyakit keganasan anak, *Sari Pediatri*, **6**(4), 176-181.

Sayuti, K., Yenrina, R., 2015, Antioksidan alami dan sintetik, ed.1, Padang: Andalas University Press.

Soebandiri, 2014, Hemopoesis, 6th ed, Jakarta: Interna Publishing.

Soekamto, S.M., Sandhika, W., and Fauziah, D., 2002, Aspek patologi tumor THT-KL. Perkembangan terkini diagnosis dan penatalaksanaan tumor ganas THT- KL. SMF Ilmu Penyakit THT-KL FK Unair/RSUD Dr. Soetomo, Surabaya.

Suryohudoyo, P., 2000, Oksidan, antioksidan dan radikal bebas. In: K*apita selekta Ilmu Kedokteran Molekul, Jakarta: Infomedika. pp. 312-347.*

Suseela, M.R., and Toppo, K., 2006, Haematococcus puvialis a green alga, richest natural source of astaxanthin, *Current Science*, **90**(12), 1602-1603.

Vokes, E.E., and Chong, N., 2008, Chemotherapy of head and neck cancer. In: Perry, M.C. editor. *The chemotherapy of source book*. Lippincot Williams & Wilkins, Philadelphia.

WHO, 2006, Global Cancer Rates Could Increase by 50% to 15 Million by 2020. Available from URL: http://www.who.int/mediacentre/news/releases/2003/pr27/en/.

Xue, X-L., Han, X-D., Li, Y., Chu, X-F., Miao, W-M., Zhang, J-L., and Fan, S-J., 2017, Astaxanthin attenuates total body irradiation-induced hematopoietic system injury in mice via inhibition of oxidative stress and apoptosis, *Stem Cell Res Ther*, **8**(1), 7.

Zulkarnain, I., Surarso, B., and Purnami, N., 2017, Decrease of haemoglobin, neutrophil, and platelet level following cisplatin-paclitaxel chemotherapy on head and neck malignancy, *Jurnal Ilmu Kesehatan Telinga Hidung Tenggorok Bedah Kepala dan Leher*, **10**(1), 1-10.