

Changes In Retina, Macula And Optic Nerve With Doxorubicin-Paclitaxel And Cisplatin-Paclitaxel Chemotherapy In Breast Cancer

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Abstract- Ocular toxicity caused by chemotherapy can be effect into the anatomical, physiological, and biochemical features of the eye. Combination use of Cisplatin, Doxorubicin, and Paclitaxel is often used for breast cancer therapy. This chemotherapy agent has been shown in several studies can cause ocular toxicity.

Method: This is a quasi experimental study. Subjects were patients with breast cancer who underwent Doxorubicin-Paclitaxel or Cisplatin-Paclitaxel chemotherapy. The examination includes visual acuity, intraocular pressure, Amsler grid test, color vision test, changes on retina, macula and optic nerve. Before, after and 3 weeks after chemotherapy.

Results: 120 eyes (60 subjects) grouped into 58 eyes with Cisplatin-Paclitaxel, and 62 eyes with Doxorubicin-Paclitaxel. There was no relationship between visual acuity and intraocular pressure Amsler grid test changes to chemotherapy. There is a significant relationship FM 100 Hue test, retinal, macula and optic nerve changes with chemotherapy.

Conclusion: Doxorubicin-Paclitaxel and Cisplatin-Paclitaxel cause changes in color vision, and also in the retina, macula, and optic nerve.

Index Terms- Chemotherapy, Cisplatin, Doxorubicin, Ocular Toxicity, Paclitaxel

I. INTRODUCTION

Chemotherapy is a treatment using drugs that aim to destroy or slow the growth of cancer cells. Chemotherapy side effects arise because the chemotherapy drugs not only destroy cancer cells but also attack healthy cells, especially cells that divide rapidly.¹

Patients with cancer or malignancy in addition to can experience the benefits of chemotherapy, will also feel the side effects or effects toksikn that ditimbukan by the administration of chemotherapy agents. chemotherapy can cause disturbances in vision function due to the presence of toxicity effects.² the Eye and adnexa can be susceptible to anticancer therapy targeted because many of the molecules is disturbed. Lesions of the posterior segment is one of the important parts because the loss of vision can occur.^{2,3} Retina is part of the ocular which is active in metabolic in the body, making it a prime target for unwanted side effects from chemotherapy agents.⁴

Side effects that occur due to the administration of chemotherapy agents due to the occurrence of the mechanism of neurotoxicity in ocular still need to be further studied, such a hypothesis due to ischemic or electrophysiological can not fully explain the pathogenesis of neurotoxicity ocular. Neurotoxicity ocular associated with the administration of chemotherapeutic agents such as Cisplatin, Doxorubicin and Paclitaxel, Although rare, several case reports previously showed that the presence of visual impairment due to the neurotoxicity that occurs due to administration of chemotherapy should be considered in treating the neoplastic disease patient, the administration of chemotherapeutic agents such want to proceed.^{5,6}

II. METHOD

This is a quasi experimental design study with control was approved by the ethics committee of Medical Faculty of Sumatera Utara University. The subjects were all patients who admitted to the Murni Teguh Hospital Medan. The subjects were all patients who was diagnosed with breast cancer from January to July 2020. Total sample was 60 people with age over 18 years. From 126 eyes, there were 6 eyes drop out from study because the patient didn't come for the second and third examinations.

This study discusses several assessments of the vision system relating to the effects that may occur in patients undergoing chemotherapy. The chemotherapy agents given are Doxorubicin-Paclitaxel and Cisplatin-Paclitaxel. The study was conducted with a assessment of visual acuity, intraocular pressure, central vision, color vision, retinal, macula and optic nerve. The assesment are before, after and 3 weeks after first chemotherapy. Visual acuity test using Snellen Chart examination, intraocular pressure using Topcon Non contact Tonometer, color vision with Farnsworth Munsell 100 Hue test, central vision function with Amsler Grid Test, Posterior Segment (retina, macula, and optic nerve) with Ullman Indirect and 20 D lens. All data is analyzed using IBM SPSS Statistic 26 for Windows.

III. RESULT

In this study there were 120 eyes examined. Previously there were 3 people (6 eyes) with drop out cases because they were not present during the second or third examination during the study. The chemotherapy agents given are Doxorubicin-Paclitaxel

and Cisplatin-Paclitaxel. The average age are 49. The youngest is 39 years old and the oldest is 69 years old. Time of diagnosis breast cancer is categorized into 3 i.e. 0 – 12, 13 – 24 and 25 – 36 months.

Table 1. Distribution Characteristics of Subjects

Characteristic	Total	%
Chemotherapy agent	31	51,7
Doxorubicin-Paclitaxel	29	48,3
Cisplatin-Paclitaxel		
Age	36	60,0
35 – 49 years	24	40,0
50 – 69 years		
Time of Cancer	46	76,7
0 – 12 month	6	10,0
13 – 24 month	8	13,3
25 – 36 month		

This study with the assessment of the function of visual acuity, intraocular pressure, central vision, color vision, retina, macula and optic nerve. Before, after 1st chemotherapy and 3 weeks after chemotherapy. In table 2. Show data about the distribution of characteristics and the relationship of the characteristics to chemotherapy, before (H_0), after 1st chemotherapy (H_1) and 3 weeks after chemotherapy (H_2).

The results of the visual acuity examination varied from normal 6/6 to < 3/60. There appeared to be an increase in the number of eyes with visual acuity category both from the time before and after chemotherapy. Statistically, with a Chi square test found that there is no relationship between visual acuity before, after first chemotherapy and 3 weeks after first chemotherapy.

The results of intraocular pressure examination obtained the value of the intraocular pressure that low of 8 mmHg and the

highest was 21 mmHg. However with fisher exact test there was no significant relationship between intraocular pressure before, after first chemotherapy and 3 weeks after first chemotherapy to the both of agent chemotherapy.

The results of the amsler grid test obtained in the study subject as a whole the subject's eyes have a normal value on the Amsler grid test results. By using chi Square test , there was no significant relationship between Amsler grid test to the two chemotherapy agents.

The FM 100 test results are categorized into 3. The superior results if the total error score is 0-16, Average 16-100 and low if the error score is > 100. In this study the result category with the most number was found in the average group before, after and 3 weeks after first chemotherapy. with chi square test, there was a significant relationship between the results of the FM 100 Hue test after first chemotherapy (FM 100 H_1) on the two chemotherapy agents (p. 0.001).

Retinal examination results found that the number of normal retina is decreasing from before, after and 3 weeks after first chemotherapy. Statistically, it was found with chi square test, there was a significant relationship between retinal characteristics after first chemotherapy (Retina H_1) to the two chemotherapy agents (p. 0.029).

The results of the examination on macula, in the normal category have a larger number than edema. The table also shows that macular edema in Cisplatin-Paclitaxel has a number of more than the Doxorubicin-Paclitaxel. However statistically, using the Chi square test showed that there is no relationship between macular before, after and 3 weeks after first chemotherapy to the two chemotherapy agents.

The results of the study on the assessment of Optic Nerve Head (ONH) using Frisen Grading obtained more normal scores compared to edema and appeared to increase the number of normal ONH before, after and 3 weeks after first chemotherapy. However, the Chi square test found that there was no association between the optic nerve head (ONH) to the two chemotherapy agents.

Table 2. Distribution Characteristic of Subject and Association between Characteristic to chemotherapy agent

Characteristic	Chemotherapy agent						P.	
	H_0		H_1		H_2			
	Doxorubicin Paclitaxel	Cisplatin Paclitaxel	Doxorubicin Paclitaxel	Cisplatin Paclitaxel	Doxorubicin Paclitaxel	Cisplatin Paclitaxel		
n (%)								
Visual Acuity								
6/6 – 6/12	35 (46,7%)	40 (53,3%)	40 (48,2%)	43 (51,8%)	39 (45,3%)	47 (54,7%)		
< 6/12 – 6/18	4 (50,0%)	4 (50,0%)	5 (50,0%)	5 (50,0%)	3 (60,0%)	2 (40,0%)	H_0 0,408	
< 6/18 – 6/60	14 (63,6%)	8 (36,4%)	10 (83,3%)	2 (16,7%)	15 (83,3%)	3 (16,7%)	H_1 0,070	
< 6/60 – 3/60	9 (64,3%)	5 (35,7%)	7 (58,3%)	5 (41,7%)	5 (50,0%)	5 (50,0%)	H_2 0,044	
< 3/60	0 (0%)	1 (100%)	0 (0%)	3 (100%)	0 (0%)	1 (100%)		
Intraocular Pressure								
< 10 mmHg	1 (100%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)	0 (0%)	H_1 0,483	
10 – 21 mmHg	61 (51,3%)	58 (48,7%)	62 (52,1%)	57 (47,9%)	61 (51,3%)	58 (48,7%)	H_2 1,000	
Amsler Grid Test								
Normal	55 (51,4%)	52 (48,6%)	60 (52,2%)	55 (47,8%)	62 (52,5%)	56 (47,5%)		
Metamorphopsia	7 (70,0%)	3 (30,0%)	1 (33,3%)	2 (66,7%)	0 (0%)	2 (100%)	H_0 0,207	
Scotoma	0 (0%)	2 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	H_1 0,490	
Metamorphopsia,Scotoma	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	H_2 0,232	
Metamorphopsia,Macropsia	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)		

FM 100 Hue Test							
Low	22 (64,7%)	12 (35,3%)	20 (83,3%)	4 (16,7%)	6 (50,0%)	6 (50,0%)	H ₀ 0,190
Average	32 (45,7%)	38 (54,3%)	32 (41,0%)	46 (59,0%)	40 (54,1%)	34 (45,9%)	H ₁ 0,001
Superior	8 (50,0%)	8 (50,0%)	10 (55,6%)	8 (44,4%)	16 (47,1%)	18 (52,9%)	H ₂ 0,790
Retina							
Normal	47 (61,0%)	30 (39,0%)	37 (56,1%)	29 (43,9%)	42 (55,3%)	34 (44,7%)	
Hemorrhage	2 (40,0%)	3 (60,0%)	8 (80,0%)	2 (20,0%)	4 (66,7%)	2 (33,3%)	
Pigmentary Changes (PC)	8 (33,3%)	16 (66,7%)	11 (31,4%)	24 (68,6%)	12 (38,7%)	19 (61,3%)	H ₀ 0,080
Cotton Wool Spot (CWS)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	H ₁ 0,029
Hemorrhage, PC	4 (33,3%)	8 (66,7%)	5 (62,5%)	3 (37,5%)	3 (50,0%)	3 (50,0%)	H ₂ 0,411
Hemorrhage, CWS	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Hemorrhage,CWS, PC	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	
Macula							
Normal	54 (50,9%)	52 (49,1%)	61 (54,0%)	52 (46,0%)	62 (53,0%)	55 (47,0%)	H ₀ 0,779
Edema	8 (57,1%)	6 (42,9%)	1 (14,3%)	6 (85,7%)	0 (0%)	3 (100%)	H ₁ 0,056
Optic Nerve Head							
Normal	57 (52,3%)	52 (47,7%)	55 (51,9%)	51 (48,1%)	58 (50,9%)	56 (49,1%)	H ₀ 0,212
Grade 1. Very early papilledema	3 (33,3%)	6 (66,7%)	4 (36,4%)	7 (63,6%)	2 (50,0%)	2 (50,0%)	H ₁ 0,279
Grade 2. Early papilledema	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	H ₂ 0,386
Grade 3. Moderate papilledema	2 (100%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	0 (0%)	

Table 3 show data about the relationship of changes in each characteristic. In this case it is assessed on the changes in the H₀H₁ and H₁H₂ on each chemotherapy agent (Doxorubicin-Paclitaxel and Cisplatin-Paclitaxel). The changes here include decreased, constant and increased categories compared when H₀ to H₁ and H₁ to H₂ for each chemotherapy agent on each characteristic.

In the changes in visual acuity, there are several changes in visual acuity. The changes here include decreased, constant and increased categories. However, statistical analysis using the Chi square test, there was no relationship between changes in H₀H₁ and H₁H₂ in the eye with the Doxorubicin-Paclitaxel or Cisplatin-Paclitaxel. At changes in intraocular pressure H₀H₁ and intraocular pressure H₁H₂ in each chemotherapy agent. However, with the Chi Square test there was no relationship between changes in intraocular pressure in H₀H₁ and H₁H₂ in the eye with Doxorubicin-Paclitaxel or Cisplatin-Paclitaxel. Amsler grid test of H₀H₁ and H₁H₂ in each chemotherapy agent. However, with the Mean Whitney test and fischer exact test there was no relationship between changes in Amsler grid test in H₀H₁.

and H₁H₂ in the eye with Doxorubicin-Paclitaxel or Cisplatin-Paclitaxel. The changes in the FM 100 Hue test results H₀H₁ and H₁H₂ on each chemotherapy agent. However, with the Chi Square test, there was no relationship between changes in FM 100 test results on H₀H₁ and H₁H₂ in the eyes with Doxorubicin-Paclitaxel or Cisplatin-Paclitaxel.

In retinal changes to chemotherapy agents, there was a change in the retina of H₀H₁ in the subject's eye to the chemotherapy agent. From the chi square test results can be seen that there is a significant relationship between changes in the retina H₀H₁ to chemotherapy agents.

Changes in macular H₀H₁ and H₁H₂ in subjects to chemotherapy agents. Mann-Whitney tests found statistically that there was a significant relationship between changes in the H₀H₁ macula to chemotherapy agents. But in H₁H₂ there was no significant macular change to the chemotherapy agent.

Changes in the optic nerves H₀H₁ and H₁H₂ in subjects against chemotherapy agents. using the Chi Square test it can be concluded that there is no relationship between changes in the optic nerve H₀H₁ and H₁H₂ to the two chemotherapy agents.

Table 3. Distribution Characteristic Changes H₀H₁ and H₁H₂ to Chemotherapy Agent

Characteristic	Time	Alteration	DoxorubicinPaclitaxel	CisplatinPaclitaxel	p.
			n (%)	n (%)	
Visual Acuity	H ₀ H ₁	Decreased	5 (45,5%)	6 (54,5%)	0,911
		Constant	35 (52,5%)	32 (47,8%)	
		Increased	22 (52,4%)	20 (47,6%)	
	H ₁ H ₂	Decreased	3 (75,0%)	1 (25,0%)	0,466
		Constant	49 (52,7%)	44 (47,3%)	
		Increased	10 (43,5%)	13 (56,5%)	
Intraocular Pressure	H ₀ H ₁	Decreased	28 (57,1%)	21 (42,9%)	0,411
		Constant	7 (38,9%)	11 (61,1%)	
		Increased	27 (50,9%)	26 (49,1%)	

		Decreased	27 (51,9%)	25 (48,1%)	
Amsler Grid Test	H_1H_2	Constant	16 (53,3%)	14 (46,7%)	0,962
		Increased	19 (50,0%)	19 (50,0%)	
		Decreased	1 (100%)	0 (0%)	
FM 100 Hue Test	H_0H_1	Constant	55 (50,5%)	54 (49,5%)	0,809
		Increased	6 (60,0%)	4 (40,0%)	
		Constant	60 (51,3%)	57 (48,7%)	
	H_1H_2	Increased	2 (66,7%)	1 (33,3%)	1,000
Retina	H_0H_1	Decreased	10 (71,4%)	4 (28,6%)	
		Constant	38 (47,5%)	42 (52,5%)	0,247
		Increased	14 (53,8%)	12 (46,2%)	
Macula	H_1H_2	Decreased	2 (20,0%)	8 (80,0%)	
		Constant	40 (54,1%)	34 (45,9%)	0,111
		Increased	20 (55,6%)	16 (44,4%)	
Optic Nerve Head	H_0H_1	Decreased	13 (65,0%)	7 (35,0%)	
		Constant	46 (53,5%)	40 (46,5%)	0,036
		Increased	3 (21,4%)	11 (78,6%)	
Optic Nerve Head	H_1H_2	Decreased	2 (66,7%)	1 (33,3%)	
		Constant	52 (50,0%)	52 (50,0%)	0,640
		Increased	8 (61,5%)	5 (38,5%)	
Macula	H_0H_1	Decreased	0 (0%)	3 (100%)	
		Constant	55 (50,9%)	53 (49,1%)	0,024
		Increased	7 (77,8%)	2 (22,2%)	
Optic Nerve Head	H_1H_2	Constant	61 (52,6%)	55 (47,4%)	
		Increased	1 (25,0%)	3 (75,0%)	0,352
		Decreased	3 (60,0%)	2 (40,0%)	
Optic Nerve Head	H_0H_1	Constant	59 (51,9%)	55 (48,2%)	0,547
		Increased	0 (0%)	1 (100%)	
		Constant	58 (52,3%)	53 (47,7%)	
	H_1H_2	Increased	4 (44,4%)	5 (55,6%)	0,737

Table 4 show data on changes in H_0H_1 to H_1H_2 for each of the chemotherapy agents (Doxorubicin-Paclitaxel and Cisplatin-Paclitaxel). Each characteristic was tested by Wilcoxon test and several changes occurred.

Changes in visual acuity show that there are negative changes that occur more in Doxorubicin-Paclitaxel than Cisplatin-Paclitaxel, but in ties (same condition) and positive changes have the same amount on both chemotherapy agents. However, statistically using the Wilcoxon test, it was found that there was no significant change between visual acuity H_0H_1 to H_1H_2 for each chemotherapy agent.

Changes in intraocular pressure for each chemotherapy agent. there are more positive changes in Doxorubicin-Paclitaxel than Cisplatin-Paclitaxel. Statistically, using the Wilcoxon test, there was no significant change between intraocular pressure H_0H_1 to H_1H_2 for each chemotherapy agent.

Changes in the Amsler grid test for each chemotherapy agent. There were more ties than negative or positive changes in both agents and statistically using the Wilcoxon test there was also no significant change between the Amsler grid test H_0H_1 to H_1H_2 for each chemotherapy agent.

Changes in FM 100 test for each chemotherapy agent, there were negative and positive changes in both agents but statistically using the Wilcoxon test there was no significant change between FM 100 test H_0H_1 to H_1H_2 for each chemotherapy agent.

However, on the retina, macula and optic nerve using the Wilcoxon test, it was found that there was a significant change in H_0H_1 to H_1H_2 with Doxorubicin-Paclitaxel.

Table 4. Distribution Characteristic Changes H₀-H₁ to H₁-H₂ Chemotherapy Agent

Characteristic	Chemotherapy	Alteration		
		Rank	n	p.
Visual Acuity	Doxorubicin-Paclitaxel	Negatif rank	20	
		Positif rank	9	0,077
		Ties	33	
	Cisplatin-Paclitaxel	Negatif rank	16	
		Positif rank	9	0,874
		Ties	33	
	Intraocular Pressure	Negatif rank	26	
		Positif rank	21	0,613
		Ties	15	
Amsler Grid Test	Doxorubicin-Paclitaxel	Negatif rank	25	
		Positif rank	16	0,349
		Ties	17	
	Cisplatin-Paclitaxel	Negatif rank	6	
		Positif rank	2	0,366
		Ties	54	
	FM 100 Hue Test	Negatif rank	4	
		Positif rank	1	0,180
		Ties	53	
Retina	Doxorubicin-Paclitaxel	Negatif rank	16	
		Positif rank	26	0,054
		Ties	20	
	Cisplatin-Paclitaxel	Negatif rank	18	
		Positif rank	20	0,994
		Ties	20	
	Macula	Negatif rank	4	
		Positif rank	16	0,005
		Ties	42	
Optic Nerve Head	Doxorubicin-Paclitaxel	Negatif rank	10	
		Positif rank	10	1,000
		Ties	38	
	Cisplatin-Paclitaxel	Negatif rank	7	
		Positif rank	1	0,034
		Ties	54	
	Cisplatin-Paclitaxel	Negatif rank	2	
		Positif rank	4	0,234
		Ties	52	

IV. DISCUSSION

Patients with cancer or malignancy may benefit from advances in chemotherapy, but chemotherapy agents also cause toxic effects. In recent years, it has been reported that chemotherapy can cause impaired vision function due to toxicity in chemotherapy.

The subjects of the study were women with an average age of 49 years with the youngest being 39 years old and the oldest being 69 years old. In line with data from the Indonesian Ministry of Health, it is high increase in the prevalence of cancer in the age group 25-34 years, 35-44 years, and 45-54 years.⁷ The chemotherapy agents given are Doxorubicin-Paclitaxel and Cisplatin-Paclitaxel chemotherapy agents. Both of these agents

are combination chemotherapy agents used in patients with breast cancer. This study was conducted by assessing visual acuity function, intraocular pressure, central vision function, color vision function, retinal condition, macula and optic nerve before, after chemotherapy and 3 weeks after chemotherapy agents. The number of eyes examined in this study amounted to 120 eyes from 60 patients. Where previously there were 3 people (6 eyes) with cases of drop out because they did not come during the second or third examination during the study. The length of time a patient suffered from breast cancer was calculated from the time of diagnosed, and in this study 46 people were categorized into 3 - 12 months, 6 people 13-24 months and 8 25 - 36 months.

In this study it was found that there was no relationship and changes between visual acuity before, after chemotherapy and 3

weeks after chemotherapy. This is in line with research by Scaioli, visual acuity with Paclitaxel chemotherapy is reported to cause blurred vision, scotoma and photopsia. In some patients, it was found when chemotherapy was started, but it can also be during and after chemotherapy. but there was no relationship between the chemotherapy protocol and the appearance of these symptoms. In his study also found no significant association with decreased visual acuity during chemotherapy.⁸

The results showed that the lowest intraocular pressure was 8 mmHg and the highest was 21 mmHg. On examination of intraocular pressure, it was found that there was no relationship and changes between intraocular pressure before, after chemotherapy and 3 weeks after chemotherapy. In line with research conducted by Berker Bakbak et al. there was no significant difference in intraocular pressure before and after chemotherapy.⁹

The results of the study to see the central vision function using the Amsler grid test, which shows that the results obtained from the amsler grid test in the study subjects were normal, Metamorphopsia, Scotoma, Metamorphopsia with Scotoma, Metamorphopsia and Macropsia. In the Amsler grid examination, it was found that there was no relationship and change between the results of the Amsler grid test before, after chemotherapy and 3 weeks after chemotherapy. This may occur because the use of Paclitaxel, as reported by Scaioli, stated in his research related to Positive Spontaneous Visual Symptoms (PSVS) on the administration of the chemotherapy agent Paclitaxel which manifests as photopsia, scotoma and impaired visual acuity, these symptoms if found, usually transient.⁸

The color vision function test using the Farnsworth Munsell 100 Hue Test, it was found that there was a significant relationship between the results of the FM 100 Hue test after chemotherapy (FM 100 H₁) on the two chemotherapy agents. This is as has been reported by Simon Dulz et al and Wilding et al researching the toxicity of the retina after giving the chemotherapy agent Cisplatin in cancer that in their study it was found that 9 eyes out of 6 patients observed during the study had color vision disorders. And in approximately 38% of patients who received Cisplatin chemotherapy, Cone and Rod had dysfunction.^{10,11}

On examination of the retina using indirect funduscopy, it was found that the retinal characteristics were Normal, hemorrhage, pigmentary changes, Cotton Wool Spot (CWS), retinal hemorrhage with pigment changes, retinal hemorrhage with Cotton Wool Spot and retinal hemorrhage, CWS with retinal pigment changes. And in this study it was found that there was a significant relationship between retinal characteristics after chemotherapy (Retina H₁), and there was a significant change in the retina H_{0H1} for both chemotherapy agents and there was a significant change in the retina H_{0H1} to H_{0H2} with Doxorubicin-Paclitaxel. Reported some research state that cancer patients undergoing chemotherapy with Cisplatin and Paclitaxel and Doxorubicin will have a toxic effect on the retinal structure. Cisplatin is an effective chemotherapy for cases with various solid tumors. Which has side effects / toxicity on the ocular system. Among them are maculopathies with a form of pigment changes caused by retinal pigment disorders, changes in color perception caused by photoreceptor dysfunction and mild retinal ischemia such as cotton wool spots and retinal hemorrhage.^{5,6,10-15}

Macular examination results obtained in this study were normal and macular edema. There is a significant relationship between H_{0H1} macular changes to chemotherapy agents and there is a significant change in H_{0H1} to H_{0H2} macular with Doxorubicin-Paclitaxel. This is in line with some research, It was found that a significant increase in macular thickness with the use of Paclitaxel was associated with an increase in macular thickness for the incidence of Cystoid macular edema due to impaired retinal blood barrier.^{16,17,18}

In this study, the results of examination on the optic nerve were found to be Normal, Grade 1. Very early papilledema, Grade 2. Early papilledema and Grade 3. Moderate papilledema which was applied through the Frisen Grading System. There was a significant change in the optic nerves head (ONH) H_{0H1} to H_{0H2} with Doxorubicin-Paclitaxel. In line with studies by Scaioli et al. Capri et al., and Caraceni et al. The occurrence of reduced amplitude of the P100 component with a slight delay in elongation, measured by VEPs in patients using Doxorubicin and paclitaxel, showed an occurrence / disturbance in the optic nerve. Reported 3 cases with visual impairment and optic nerve disorders on Paclitaxel use.^{15,19,20}

However, in our study there are still limitations such as classifying chemotherapy doses, short administration times (chemotherapy cycles) and searching for causes of abnormalities that occur before chemotherapy that may be related to the incidence of Cancer Associated Retinopathy.

V. CONCLUSION

Patient with breast cancer undergoing chemotherapy should be ocular examination before, during and after chemotherapy. From our study that grouped into 58 eyes with Cisplatin-Paclitaxel, and 62 eyes with Doxorubicin-Paclitaxel. We found there was no relationship between visual acuity, intraocular pressure and Amsler grid test changes to chemotherapy. There is a significant relationship FM 100 Hue test, retinal, macula and optic nerve changes with chemotherapy. Doxorubicin-Paclitaxel and Cisplatin-Paclitaxel chemotherapy cause changes in color vision, and also in the retina, macula, and optic nerve.

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