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Original Article

The Effect of Vitamin E on Oral Mucositis Induced by Chemotherapy in Non-Hodgkin Lymphoma Patients Receiving Chemotherapy

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ABSTRACT

Chemotherapy-induced mucositis is a side effect of chemotherapy that often occurs in patients with solid tumors and lymphoma. Oral mucositis can affect nutritional status and the risk of infection, both local and systemic. Antioxidant Vitamin E is beneficial for the prevention and therapy of both oral and gastrointestinal mucositis. **Aim:** To determine the effect of vitamin E therapy on the incidence of oral mucositis in non-Hodgkin lymphoma (NHL) patients receiving chemotherapy. **Methods:** This is a single blind experimental study in 62 NHL patients undergoing chemotherapy who meet the inclusion criteria. Patients who met the inclusion criteria were randomly divided into 2 groups, namely 31 patients (treatment group) received vitamin E 400 mg / IU per day for 7 days and 31 patients in the placebo group. The incidence and grade of oral mucositis were observed on day 7. Statistical analysis used Chi Square and Mann Whitney test according to the data type. **Results:** a total of 67% NHL patients were male, most of whom were over 46 years of age and as many as 50% of patients used chemotherapy regimens RCHOP and CHOP. There was an incidence of oral mucositis in 35% in the placebo group and 12.9% in the treated group (p = 0.038). In the placebo group there were 4.8% of patients with grade 2 and 3 oral mucositis, which were not found in the therapy group. **Conclusion:** treatment with vitamin E in NHL patients undergoing chemotherapy can prevent chemotherapy-induced oral mucositis and prevent its severity.

Keywords: oral mucositis, chemotherapy, vitamin E, non-Hodgkin's lymphoma

INTRODUCTION

Chemotherapy-induced mucositis is an erythematous and ulcerative lesion of the oral mucosa observed in patients with cancer treated with chemotherapy, and / or with radiation therapy. Oral mucositis lesions are often very painful and can affect nutrition and oral hygiene and can increase the risk of developing both local and systemic infections. Mucositis can also affect other areas of the digestive tract; for example, gastrointestinal (GI) mucositis which can manifest as diarrhea. Thus, it is clear that the effect of mucositis is very significant on the quality of life of patients. Likewise, the presence of mucositis often requires limiting the dose of cancer therapy. [1,2]

One study reported the incidence of oral mucositis in 303 of 599 patients (51%) with solid tumors or lymphoma who received chemotherapy.[25] Oral mucositis developed in 22% of 1236 chemotherapy cycles, whereas GI mucositis occurred in 7% of chemotherapy cycles.[25] The incidence of mucositis is also influenced by the dose of chemotherapy. In hematopoietic cell transplant patients who receive high doses of chemotherapy, the incidence of mucositis is around 75-80%. [3,4]

Chemotherapy-induced mucositis causes significant pain which can affect nutritional intake, oral hygiene and quality of life. Infections associated with oral mucositis lesions can lead to life-threatening systemic infections. Moderate to severe chemotherapy-induced mucositis correlated with infection-related mortality. In patients with solid tumors or lymphoma who received chemotherapy and developed mucositis, the degree of infection during the cycle was two times higher and was directly proportional to its severity compared with the group without mucositis. Infection-related deaths during chemotherapy cycles are more common in patients with oral or GI mucositis. Likewise, the mean duration of stay during chemotherapy was significantly longer in patients with mucositis. The incidence of chemotherapy dose reduction in subsequent cycles was two times higher in patients with mucositis than without mucositis.[5]

The pain from mucositis causes eating disorders by mouth, so it is often necessary to get nutrition via gastrostomy or intravenous lines. Patients with oral mucositis were significantly more likely to have a more severe condition with a weight loss of more than 5%.[5,8] In terms of medical costs, there is a significant difference between patients with mucositis and without mucositis. Patients without mucositis required an inpatient fee of approximately $3893 per chemotherapy cycle, with oral mucositis $6277 per cycle whereas those with oral and GI mucositis were $9132 per cycle. [3,4]

So based on the above conditions, it seems that prevention of mucositis is important. Various attempts have been made, but until now they have not yielded satisfactory results. Based on the role of oxidants in the mucositis process, Vitamin E which is known to have antioxidant properties in the inflammatory [7,8] process is expected to prevent mucositis in solid tumor patients undergoing chemotherapy.

METHODS

Study Design

This study is a single blind clinical trial with random sampling which aims to determine the incidence of oral mucositis in NHL patients receiving chemotherapy. The research subjects were 62 NHL patients who

met the inclusion criteria. Subjects were divided randomly into 2 groups, namely the treatment group and the control group (placebo) each of 31 patients. The inclusion criteria were NHL patients who were undergoing chemotherapy, were over 16 years of age, were not experiencing mucositis, and were willing to sign an informed consent to participate in the study.

Subsequently, subjects who met the inclusion criteria were subjected to an anamnesis regarding their main complaints, medical history and previous therapy as well as a general physical examination, including awareness, vital signs, examination of the head, neck, chest, lungs, heart, stomach, and extremities. Then the patients in the treatment group were given vitamin E and the placebo group was given placebo therapy for 7 days which was physically the same as vitamin E. On the 7th day of chemotherapy, the patients were examined to assess the incidence of oral mucositis and the degree of mucositis. This study has received approval from the Health Research Ethics Commission dr. Saiful Anwar by number 400/282/K.3/302/2019.

Statistical analysis

Statistical analysis using statistical tools, IBM *Statistical Products and Service Solutions Statistics* (SPSS) *version 25.0 for Windows.* Data were analyzed using Chi Square test and Mann Whitney test according to the type of data.

RESULTS

Characteristics of subjects

The proportion of the incidence of oral mucositis between men and women was not significantly different, namely 26.2% in men and 25.0% in women. Based on age, it was found that the highest incidence of oral mucositis was in the age group over 46 years (61.3%), whereas proportionally the incidence of oral mucositis was higher in the 26-45 years age group than in the 45-45 years age group (46.7% vs 26.7%; p <0.05) **(Table 1)**.

Table 1. Characteristics of Subjects

Variables		Oral mucositis (n)		Amount (n, %)
		(+)	(-)	
Sex	Male	31	11	42 (67.7)
	Female	16	4	20 (32.3)
Age (range)	16-25	2	0	2 (3.2)
	26-45	15	7	22 (35.5)
	>45	30	8	38 961.3)
chemotherapy regimen	CEOP	0	1	1 (1.6)
	CHOP	14	6	7 (35.5)
	COP	1	0	1 (1.6)
	RCEOP	7	0	7 (11.3)
	RCHOP	23	7	30 (48.4)
	RCOP	2	1	3 (4.8)

** R, rituximab; C, cyclophosphamide; H, hydroxydaunorubicin (doxorubicin) hydrochloride; O, oncovin (vincristine); P, prednisone*

Table 2. incidence of Oral Mucositis between Placebo and Therapy Groups

	Placebo group (n=31) n (%)	Vitamin E group (n=31) n (%)	P value
(+)	11 (35.0)	4 (12.9)	0.038*
(-)	20 (65.0)	27 (87.2)	

**Chi-Square test*

Table 3. The severity of oral mucositis between the placebo and therapy groups

Severity of oral mucositis	Placebo group (n=31) n (%)	Vitamin E group (n=31) n (%)	Total (n=62)
0	20 (32.2)	27 (43,5)*	47 (75,8)

1	4 (6,5)	4 (6,5)	8 (12.9)
2	4 (6,5)	0 (0)	4 (6.5)
3	3 (4,8)	0 (0)	3 (4.8)

**Chi-Square test*

Based on **Table 3**, it shows the incidence of oral mucositis was found in 15 (24%) patients of the total patients who underwent chemotherapy. The highest degree of mucositis was grade 0 as much as 47 (75.8%) and the lowest degree of mucositis was grade 3 as many as 8 patients (4.8%). In the vitamin E therapy group, the proportion of grade 0 oral mucositis was significantly different compared to the placebo group (43.5% vs 32.2%; p <0.05) and there was no grade 2 and 3 oral mucositis (**Table 3**).

Table 4. Correlation between Vitamin E T herapy and degree of oral mucositis.

	Mean Ranks		**p value**
	Placebo group (n=31)	Vitamin E group (n=31)	
Severity of oral mucositis	35,45	27,55	0,021 *

**Mann-Whitney test*

Based on **Table 4**, there is a significant difference in the degree of mucositis in the placebo group compared to the treatment group (p=0.021).

DISCUSSION

The age range of the subjects in this study was 18-79 years with the largest age being over 46 years. This is consistent with a study that reported the largest incidence of NHL was at the age of 35-65 years. [11,12] (**Table 1**).

Based on data in the UK in 2012 the incidence of NHL (Non-Hodgkin Lymphoma) increases with older age. The American Cancer Society in 2019 also stated that the risk of developing NHL increases at older people over 65 years compared to younger ages.[13]

Based on available evidence, it has been shown that an increased incidence of chemotherapy-induced mucositis in elderly patients is associated with changes that accumulate with time, affecting both genetic and environmental causes. The presence of prolonged exposure to carcinogens in the elderly and increased risk of epigenetic gene mutations, telomere dysfunction, limited replication potential, altered environment, apoptosis, all contribute to the changing environment leading to chemotherapy-induced mucositis.[14]

Other studies have also shown that the incidence of chemotherapy-induced oral mucositis is higher at older ages (over 45 years) compared to younger ages.[15] In accordance with the results of this study, the highest incidence of chemotherapy-induced oral mucositis was found at the age above 45 years or about 50% of the total sample.

In this study, there were more male than female patients (61.7% vs 32.3%) (**Table 1**). Sex differences in the incidence of NHL were related to differences in epidemiology, clinical features and response to therapy. The incidence of NHL in the last 20 years shows that the incidence rate for the male sex is significantly higher than that for the female gender. Clinical characteristics are also different, in women the predominant location of NHL in extra nodals such as mother, thyroid and respiratory system, while related to therapy response, in women the response to

therapy with anti-CD 20 or rituximab was better than men.[18]

Chemotherapy-induced mucositis in this study was found to be more in male patients than female patients. Previous studies have shown that gender is considered to be a factor influencing the incidence of mucositis although some studies have shown conflicting results.

The effect of sex hormones has been investigated in vitro and resulted in a theory about the direct effect of estrogen on the cell proliferation process or the effect on the anti-tumor response on the female immune system is thought to be responsible for explaining the decrease in the incidence of chemotherapy-induced mucositis in women.[20] Another mechanism thought to be related to the effects of estrogen is the immune response. The study found that 17β-estradiol spontaneously decreased the production of IL6 by MN cells resulting in lower levels of IL6. Meanwhile, high IL6 levels are associated with the incidence of chemotherapy-induced mucositis.[20] Estrogen exerts a protective effect by lowering IL6 (Interleukin-6) levels. Immunological effects that are not directly related to sex hormones were also explored. Helper T cells are essential for the body's immune response. T Helper 1 (TH1) cells secrete cytokines that promote cellular immunity to fight intracellular pathogens while T helper 2 cells (TH2) control humoral immunity by regulating antibody production. Unbalanced regulation and expression of cytokines TH1 and TH2 play an important role in the development of chemotherapy-induced mucositis.[23] Another proposed mechanism is through the direct effect of estrogen on all types of lymphocytes that express estrogen receptors. The mechanism of estrogen inhibition on cell proliferation is unclear, but it is thought to play a role in chemotherapy-induced mucositis.[24] Based on the information above, it can be concluded that the gender factor in the incidence of mucositis still causes controversy, so in this study gender cannot be ruled out as a confounding factor.

Doxorubicin-based chemotherapy remains the gold standard of first-line NHL therapy. In this study the CHOP regimen was administered to 14 (22.5%) patients, whereas the COP regimen was administered to only 1 (1.2%) patient. The LNH management guidelines recommend CHOP as the regimen of first choice in LNH patients. [35]

Doxorubicin is a drug belonging to the anthracycline class that has the potential to cause chemotherapy-induced mucositis. There are two mechanisms of doxorubicin activity against cancer cells, the first is through the intercalation bond into DNA which interferes with the work of 2-topoisomerase which is useful in the DNA replication process and the second is through the formation of free radicals to damage cell membranes, DNA, and proteins.[26] Doxorubicin is oxidized to semiquinone, an unstable metabolite which is converted back to doxorubicin. This conversion process releases ROS (Reactive Oxygen Species) which can result in fat peroxidation and damage to membranes, DNA, oxidative stress, and triggers apoptosis from cells. Gene candidates that regulate this conversion process involve enzymes that can carry out oxidation reactions (NADH dehydrogenase, nitric oxide synthase, xanthine oxidase) and deactivate glutathione peroxidase, catalase, superoxide dismutase.[6] There is another possibility that doxorubicin can enter the

nucleus and interfere with 2-topoisomerase which results in DNA damage and cell death.[26]

Doxorubicin is a cytostatic drug which also often causes serious side effects in the form of mucositis. Doxorubicin acts primarily at the DNA level by forming covalent bonds to DNA and is associated with increased apoptosis of actively multiplying cells which ultimately leads to inhibited proliferation of new mucosal cells. This condition supports the occurrence of mucositis due to chemotherapy in patients.[26]

Another agent is Cyclophosphamide (CYC). Cyclophosphamide is a chemotherapy agent with alkylating activity related to nitrogen that binds to DNA and interferes with mitosis and cell replication. CYC targets rapidly dividing cells and is often used in antineoplastic management in the context of solid tumor and hematological malignancies. CYC has been shown to be effective in the treatment of lymphoma, leukemia, multiple myeloma, breast cancer, ovarian adenocarcinoma, retino-blastoma, neuroblastoma, nephritic syndrome in children, and others. Cyclophosphamide also has immunosuppressive effects in addition to anti-mitotic and anti-replication effects. Specifically, CYC induces suppression of cellular and humoral immunity through its action on T and B cells. [32] The activity of cyclophosphamide as an immunosuppressant agent is derived from its ability to kill proliferating lymphocytes, including natural killer cells, T cells, and B cells, all of which are sensitive to cyclophosphamide.[32]

Some other chemotherapy agents that have been shown to have high mucosal toxicity are daunorubicin, ara-C, etoposide, cyclophosphamide, doxorubicin, idarubicin and busulfan / melphalan.[32]

Based on the results of this study, it was found that the regimen using doxorubicin caused the most chemotherapy-induced mucositis (CHOP and RCHOP) so it was suspected that doxorubicin might play an important role in the incidence of oral mucositis.

Effect of Vitamin E on Chemotherapy-Induced Mucositis

Chemotherapy-induced oral mucositis is defined as the appearance of ulcerated lesions in the mouth area after chemotherapy. Oral mucositis appears on day 1-14, influenced by many factors including nutritional status, comorbidities such as metabolic diseases (DM, CKD), viral, bacterial and fungal infections. In this study patients with previous mucositis were excluded from the study. The examination of the incidence of mucositis which was checked on the 7th day of chemotherapy showed that the incidence of chemotherapy-induced mucositis occurred on the 7th day of chemotherapy drug administration. This condition is in accordance with the theory of the nadir point of chemotherapy agents, namely the 7th day of chemotherapy agents at the lowest point of the immune system. usually characterized by the onset of neutropenia in the patient.[29]

This study showed that the administration of vitamin E significantly reduced the incidence of chemotherapy-induced oral mucositis in NHL patients undergoing chemotherapy **(Table 2).** The ability of vitamin E to protect epithelial cells thereby reducing the degree of mucositis is due to its ability to increase the order of the lipid structure of the cell membrane to become tighter. Free radicals make the membrane phospholipid its main target and in this case

vitamin E efficiently prevents the peroxidation of fat in the cell membrane. Therefore, vitamin E improves the quality of cell membrane recovery by preventing the formation of oxidized phospholipids that can interfere with the fusion of the cell membrane.[28]

The effect of vitamin E on the degree of chemotherapy-induced mucositis

The degree of chemotherapy-induced oral mucositis was higher in the placebo group than in the vitamin E group **(Tables 3 and 4).** This is similar to the study of alpha tocopherol administration in the incidence of chemotherapy-induced mucositis in patients where the results of the treatment group were lighter in degree than the placebo group. The study stated that patients in the placebo group had grade 1, 2, 3 and 4 mucositis, while the treatment group only experienced grade 1, 2 and 3 mucositis without anyone getting grade 4 mucositis.[26]

Factors affecting the degree of chemotherapy-induced oral mucositis include complaints of pain in the oral cavity before chemotherapy and lack of attention to oral hygiene before, during and after chemotherapy. Additional risk factors are the type of cancer, the location of the cancer, the antineoplastic substance used, the dose, the administration schedule, the radiation area, and the patient's age.[30]

As previously explained, vitamin E can act as an anti-oxidant or anti-inflammatory in chemotherapy-induced mucositis. One way to further explain whether the antioxidant mechanism underlying the decrease in the incidence of mucositis due to chemotherapy requires examination of the antioxidant marker, namely Malondialdehyde (MDA). MDA is the end product of lipid oxidation. High levels of MDA are influenced by levels of lipid peroxidation, which indirectly also indicates a high number of free radicals. Free radicals are highly reactive, can cause biochemical changes and damage various components of living cells such as proteins, lipids, carbohydrates, and the nucleus of the cell membrane which consists of lipid components.[35]

Limitations of the study

Some of the limitations of this study were the uneven proportion of patients based on age, type of chemotherapy and duration of chemotherapy for each subject so that they could not control for this as a confounding factor. Besides, adherence to taking vitamin E in the study subjects was only assessed based on anamnesis.

CONCLUSION

Patients with NHL who are receiving chemotherapy, giving Vitamin E can prevent oral mucositis. Giving vitamin E can also reduce the degree of chemotherapy-induced oral mucositis.

More specific research is needed regarding chemotherapy regimens and duration of chemotherapy on the incidence of chemotherapy-induced mucositis and further research related to the factors that influence the occurrence of chemotherapy-induced mucositis.

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