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Evaluation of oral mucositis in pediatric cancer patients in Hiwa Hospital in Sulaymaniyah city, Kurdistan Region, Iraq

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Abstract

Background and objective: Oral mucositis is caused by the destruction of the oral mucosal epithelium and suppression of its growth secondary to antineoplastic treatment in the form of chemotherapeutic drugs, substances, or radiotherapy. This study aimed to evaluate oral mucositis in pediatric cancer patients because it is one of the common side effects of cancer therapy that influences the outcome.

Methods: This is a cross-sectional study that enrolled 100 pediatric patients with both hematological and non-hematological cancer. The age of the patients ranged from 1-18 years, involving both genders. Cases admitted to Hiwa hospital were clinically evaluated for oral mucositis, and ethical permission was taken from parents. Risk factors were assessed, including age, sex, cancer type, type of chemotherapy, radiotherapy, number of cycles, complete blood count, interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha, and tumor necrosis factor-beta.

Results: Baseline serum cytokines levels showed significant correlation between Interleukin-6 and intensity of the oral mucositis (P = 0.003, rho = 0.314) and no correlation between severity of oral mucositis with tumor necrosis factor-alpha, tumor necrosis factor-beta nor interleukin-1 beta (P = 0.140 and rho = 0.258, P = 0.463 and rho = -0.079, and P = 0.706 and rho = -0.041, respectively). There was significant relationship between hemoglobin level, neutropenia and type of non-hematological cancer with the intensity of oral mucositis respectively ($P \leq 0.001$ and rho = -0.352, P = 0.027 and rho = -0.221, and P = 0.035 and rho = 0.095, respectively). Correlation between age, gender, white blood cell count, platelet count, type of hematological malignancy and past history with the intensity of the oral mucositis did not show significant result.

Conclusion: Intensity of oral mucositis increased with anemia, neutropenia, high interleukin-6 level, and the type of non-hematological cancer. It is recommended to treat anemic, neutropenic patients as soon as possible before exacerbating the mucositis. Methotrexate is the most aggressive drug alone and in combined chemotherapy agents, which may cause mucositis and needs prophylaxis like topical nystatin suspension or other methods.

Keywords: Oral mucositis; Pediatric cancer; Non-hematological; Hematological; Sulaymaniyah.

Introduction

Oral mucositis, also called mucosal barrier injury, is the term given to the widespread erythema, ulceration, and soreness that commonly complicates a number of therapeutic procedures involving chemotherapy, radiotherapy, or chemoradiotherapy, used largely in the treatment of cancer but also in the conditioning prior to bone marrow transplantation (i.e., hematopoietic stem cell transplantation).[1] Oral mucositisis the

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single most debilitating complication of high -dose chemotherapy and radiation therapy to the head and neck. In addition to significant local discomfort, mucositis may be associated with an increased need for total parenteral nutrition, prolonged hospital stays, and, most importantly, systemic bacteremia and sepsis.[2] In addition to chemotherapy-induced nausea and vomiting, oral mucositisis one of the most common and distressing side effects of cancer therapy. Mucositis occurs secondary to damage of gastrointestinal mucosal lining from chemotherapy and radiotherapy with a continuum from limited mildly sore erythematous mucosae to diffuse areas of painful ulceration with pseudo-membrane formation.[2,3]

Potential effects of mucositis include fever, pain, dysphagia, delay in delivery of chemotherapy and radiotherapy, anorexia resulting in malnutrition and need for nasogastric tube feeding or total parenteral nutrition, increased hospitalization, an overall decrease in quality of life, as of painful ulceration with pseudomembranous formation. Risk factors for the development of oral mucositis include stem cell transplantation, allogeneic> autologous transplantation, radiotherapy especially high dose (i.e., >50 Gray) given to the head and neck, combination chemotherapy and radiotherapy, existing oral or dental disease, altered nutritional status and previous history of mucositis.[3]

Initiation occurs with the onset of chemotherapy or radiotherapy and subsequent, direct cell damage as well as the development of reactive oxygen species, which cause further and more significant cell damage. The primary damage response leads to the expression of NF-41 (Nuclear Factor), which subsequently stimulates pro-inflammatory cytokines including INF-0 (Intermediate range Nuclear Factor), IL-6 (Interleukin), and IL-10 and results in apoptosis of the epithelial basal cells.[1,3]

The majority of bacterial infections are caused by opportunistic aerobic gram-negative bacilli that are seldom pathogenic in an immune-competent host. Other bacterial etiologies of mucositis include Klebsiella, Enterobacter, Serratia, Proteus, and Escherichia coli. Viral infections include the herpes simplex virus, the most common one, followed by cytomegalovirus, varicella zoster, and Epstein-Barr virus. The most common oral mucous super infection is caused by Candida albicans (e.g., thrush), although other Candida species may be the causative agent. The incidence of oral candidiasis is variable and influenced by the underlying disease, immune status, intensity of cancer therapy, and salivary gland function.[1,4]

This study aimed to evaluate the severity of oral mucositis in pediatric cancer patients (the hematological and non-hematological), find the relationship between the grade of mucositis severity with the type of cancer, hematological or non-hematological, and assess the relationship between cytokines level in the different stages of oral mucositis.

Methods

A cross-sectional study that enrolled One hundred pediatric patients with oral mucositis were recruited in Hiwa h ospital (Hemato-Oncological center) in Sulaymaniyah, Iraq, from the first of August 2017 to the first of February 2018. All recruited patients were approached when they had oral mucositis. All were between 1 to 18 years old, and they were identified from history and examination. Information about age, gender, body mass index, previous history of mucositis, type of chemotherapy received, type of treatment, and prophylaxis.

Inclusion criteria included 1-18 years old of both genders, hematological cancer acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and non-hematological cancer patient (solid tumor). The blood tests were taken after receiving chemotherapies and

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when the patient had developed oral mucositis. Out of the total cases of solid tumors, there were seven cases of neuroblastoma who had undergone bone marrow transplantation during study participation.

Exclusion criteria included patients below one year old (not cooperative for examination and taking blood sample) and above 18 years old, and oral mucositis in patients without cancer.

All patients' oral cavities were examined by a pediatrician for assessing the grade of oral mucositis after taking permission from their parents. The oral mucositis in all patients was developed in a period between 5 days to 2 weeks, grading done according to the World Health Organization classification.[3] Two blood samples were taken from patients, one for CBC and the other for doing TNF alpha, TNF beta, IL-1 and IL-6. The tests were done in a private laboratory in Sulaymaniyah as the device of ELISA was not available at Hiwa hospital. The kits' names included Human TNF alpha, Human TNF beta, Human IL-1 and Human IL-6 kits, respectively from (Elabascience Company). The normal value of TNF beta (0-15 pg/ml), IL-6 (0-30 pg/ml), TNF alpha (0-10 pg/ml), and IL-1 beta (<7-8 pg/ml) respectively.

There are difficulties in assessing the young, uncooperative child. The grades of oral mucositis were based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Grade 1 included asymptomatic or mild symptoms not requiring intervention.

Grade 2 included moderate pain not interfering with oral intake or requiring dietary modifications.

Grade 3 included severe pain interfering with oral intake.

Grade 4 included life-threatening consequences requiring urgent intervention.

Grade 5 included death.[3] Our patients were treated with modulation of cancer treatment if possible and giving topical nystatin suspension or chlorhexidine mouthwash with other supportive measures.

Statistical analysis: it was performed by using the IBM SPSS (version 20). A *P* value of ≤0.05 was considered statistically significant.

The Pearson Chi-square test was used to determine the significance of the relationship between independent and dependent variable pairs. The Spearman correlation coefficient was used to assess the strength of correlation between the two variables.

Results

In our study, males (61%) were more common than females (39%), with a male to female ratio of 1.56:1. Around half of patients were from outside Sulaymaniyah (47%), while 28% were from Sulaymaniyah center and 25% were from peripheral areas of Sulaymaniyah.

The effect of hemoglobin on the intensity of oral mucositis was significantly and negatively correlated (*P* <0.001, rho = -0.352). Also, the level of ANC (Absolute neutrophil count) was negatively significantly related to mucositis severity (rho = -0.221, *P* = 0.027), meaning a reduction of ANC increased the severity of mucositis due to a decrease in immunity. However, the level of WBC and platelets counts in relation to oral mucositis severity was not significantly related, as shown in Table 1.

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Table 1 Correlations between some hematological data and mucositis intensity

Hematological Data		Stage of mucositis				Total No. (%)	*P* value*	Spearman rho Correlation coefficient (*P* value)
		Stage 1 No. (%)	Stage 2 No. (%)	Stage 3 No. (%)	Stage 4 No. (%)			
Hb Level gm/dL	<5 Severe Anemia	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0.043	*P* <0.001 rho = -0.352
	5-10 Moderate anemia	15 (22.0)	31 (45.6)	14 (20.6)	8 (11.8)	68 (100.0)		
	10.1-12 Mild anemia-normal	13 (54.2)	9 (37.5)	1 (4.2)	1 (4.2)	24 (100.0)		
	>12 Normal	4 (57.1)	2 (28.6)	1 (14.3)	0 (0.0)	7 (100.0)		
WBC groups (×109 /L)	<1 Severe leukopenia	13 (22.8)	25 (43.8)	11 (19.3)	8 (14.0)	57 (100.0)	0.288	*P* = 0.503 rho = -0.068
	1-3.9 Moderate – mild leukopenia	16 (47.0)	12 (35.3)	5 (14.7)	1 (2.9)	34 (100.0)		
	4-11.9 Normal	2 (33.3)	4 (66.7)	0 (0.0)	0 (0.0)	6 (100.0)		
	≥12 leukocytosis	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	3 (100.0)		
Absolute neutrophil count (/mm3)	0-500	15 (24.2)	27 (43.5)	12 (19.3)	8 (12.9)	62 (100.0)	0.013	*P* = 0.027 rho = -0.221
	501-1000	2 (20.0)	8 (80.0)	0 (0.0)	0 (0.0)	10 (100.0)		
	1001-1500	7 (77.8)	2 (22.2)	0 (0.0)	0 (0.0)	9 (100.0)		
	>1500	8 (42.1)	5 (26.3)	5 (26.3)	1 (5.3)	19 (100.0)		
Platelet counts (×109 /L)	0-50 Severe thrombocy-topenia	16 (28.8)	24 (42.8)	10 (17.8)	6 (10.7)	56 (100.0)	0.693	*P* = 0.170 rho = -0.138
	51-100 Moderate	3 (17.6)	9 (52.9)	4 (23.5)	1 (5.9)	17 (100.0)		
	101-150 Mild	4 (50.0)	2 (25.0)	1 (12.5)	1 (12.5)	8 (100.0)		
	>150 normal	9 (47.4)	7 (36.8)	2 (10.5)	1 (5.3)	19 (100.0)		
Total		32 (32.0)	42 (42.0)	17 (17.0)	9 (9.0)	100 (100.0)	—	—

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Due to limited facilities in laboratory tests, only 89 patients were sent for IL-6, TNF-alpha groups, and TNF-beta groups, while only 88 patients were sent for IL-1 beta groups. Only IL-6 showed significant association with the intensity of oral mucositis (*P* = 0.003, rho = 0.314), as shown in Table 2.

Table 2 Correlations between cytokines and mucositis intensity

Cytokines		Stage of mucositis				Total No.(%)	*P* values*	Spearman rho Correlation coefficient (*P* value)
		Stage 1 No. (%)	Stage 2 No. (%)	Stage 3 No. (%)	Stage 4 No.(%)			
IL-6 (pg/ml)	Normal	18 (58.1)	13(37.1)	2 (13.3)	2 (25.0)	35 (39.3)	0.023	*P* = 0.003 rho = 0.314
	Abnormal	13 (41.9)	22 (62.9)	13 (86.7)	6 (75.0)	54 (60.7)		
	Total	31 (100.0)	35 (100.0)	15 (100.0)	8 (100.0)	89 (100.0)		
TNF-alpha groups (pg/ml)	Normal	9 (29.0)	19 (54.3)	9 (60.0)	5 (62.5)	42 (47.2)	0.088	*P* = 0.140 rho = -0.258
	Abnormal	22 (71.0)	16 (45.7)	6 (40.0)	3 (37.5)	47 (52.8)		
	Total	31 (100.0)	35 (100)	15 (100.0)	8 (100.0)	89 (100.0)		
TNF-beta groups (pg/ml)	Normal	17 (54.8)	21 (60.0)	10 (66.7)	5 (62.5)	53 (59.6)	0.889	*P* = 0.463 rho = -0.079
	Abnormal	14 (45.2)	14 (40.0)	5 (33.3)	3 (37.5)	36 (40.4)		
	Total	31 (100.0)	35 (100.0)	15 (100.0)	8 (100.0)	89 (100.0)		
IL-1 beta groups (pg/ml)	Normal	25 (80.7)	32 (91.4)	11 (78.6)	7 (87.5)	75 (85.2)	0.550	*P* = 0.706 rho = -0.041
	Abnormal	6 (19.3)	3 (8.6)	3 (21.4)	1 (12.5)	13 (14.8)		
	Total	31 (100.0)	35 (100.0)	14 (100.0)	8 (100.0)	88 (100.0)		

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There are 61 patients presented with hematological cancers from 100 patients and the remaining (39) patients with non-hematological cancers. Besides, the types of non-hematological cancers were significantly correlated with the severity of mucositis (*P* = 0.035, rho = 0.095).

The most non-hematological cancer that related to more severe oral mucositis has been found in neuroblastoma, while brain tumor has been related more with stage I and II (Table 3).

The effect of chemotherapeutic agents was variable regarding the stage of mucositis. Some chemotherapy alone caused significant oral mucositis, such as methotrexate and cytarabine in high doses. Some other chemotherapeutic agents caused oral mucositis combined with other chemotherapeutic agents, as shown in Table 4.

Table 3 Severity of oral mucositis by type of cancer

Type of cancer		Stage of mucositis No. (%)				Total No. (%)	*P* values*	Spearman rho Correlation coefficient (*P* value)
		Stage 1	Stage 2	Stage 3	Stage 4			
Hematological	ALL	14 (31.1)	22 (48.8)	6 (13.3)	3 (6.7)	45 (100.0)	0.363	*P* = 0.564 rho = -0.058
	AML	4 (57.1)	2 (28.6)	1 (14.3)	0 (0.0)	7 (100.0)		
	HL	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)		
	NHL	3 (37.5)	1 (12.5)	3 (37.5)	1 (12.5)	8 (100.0)		
	Total	21 (34.4)	25 (41.0)	11 (18.0)	4 (6.6)	61 (100.0)		
Non-hematological	Brain	4 (36.4)	5 (45.5)	2 (18.2)	0 (0.0)	11 (100.0)	0.027	*P* = 0.035 rho = 0.095
	Ewing sarcoma	0 (0.0)	6 (100.0)	0 (0.0)	0 (0.0)	6 (100.0)		
	Osteogenic sarcoma	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	2 (100.0)		
	Neuroblastoma	2 (18.2)	2 (18.8)	3 (27.3)	4 (36.4)	11 (100.0)		
	Willms tumor	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)		
	Rhabdomysarcoma	2 (40.0)	3 (60.0)	0 (0.0)	0 (0.0)	5 (100.0)		
	Nasopharyngeal cancer	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	2 (100)		
	Total	11 (28.2)	17 (43.6)	6 (15.4)	5 (12.8)	39 (100.0)		

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Table 4 Relationship between the types of chemotherapy-radiotherapy and mucositis intensity.

Type of chemotherapy and radiotherapy	Stage of mucositis No. (%)				Frequency (total) No. (%)	*P* value*
	Stage 1	Stage 2	Stage 3	Stage 4		
1	1 (33.3)	1 (33.3)	0 (0.0)	1 (33.3)	3 (100.0)	0.211
2,3,4	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	1 (100.0)	
5,6,15	2 (18.2)	7 (63.6)	0 (0.0)	2 (18.2)	11 (100.0)	
7,8	1 (14.3)	2 (28.6)	1 (14.3)	3 (42.9)	7 (100.0)	
1,3,9	3 (100)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	
1,10	0 (0.0)	1 (100)	0 (0.0)	0 (0.0)	1 (100.0)	
1.12.13	0 (0.0)	0 (0.0)	1 (100)	0 (0.0)	1 (100.0)	
14	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	
13	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	3 (100.0)	
6	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	
11	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	
3,22	4 (40.0)	5 (50.0)	1 (10.0)	0 (0.0)	10 (100.0)	
1,13	1 (33.3)	1 (33.3)	0 (0.0)	1 (33.3)	3 (100.0)	
13,20	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	2 (100.0)	
17,18	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	
1,3,10	3 (30.0)	5 (50.0)	2 (20.0)	0 (0.0)	10 (100.0)	
3,4,16	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	3 (100.0)	
1,3,4	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	3 (100.0)	
1,8,21	0 (0.0)	0 (0.0)	1 (100.0)	0 (0%)	1 (100.0)	
1,3,13	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	
3,9,14	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	
4,14,15	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	
1,4,10,13	2 (25.0)	5 (62.5)	1 (12.5)	0 (0.0)	8 (100.0)	
1,3,9,10	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)	4 (100.0)	
1,6,9,13	1 (25)	3 (75.0)	0 (0.0)	0 (0.0)	4 (100.0)	
1,3,10,13	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	4 (100.0)	
3,4,14,16	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	
3,5,14,19	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	
1,3,4,10,13	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)	
1,3,12,13,14	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	
1,3,9,10,13	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	
1,3,9,10,14	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	
1,3,9,10,20	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	
1,3,4,13,14	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	2 (100.0)	
1,3,4,13,14,15	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	
Total	**32 (32.0)**	**42 (42.0)**	**17 (17.0)**	**9 (9.0)**	**100 (100.0)**	

1= Methotrexate; 2= Cisplatin; 3= Vincristine; 4= Cyclophosphamide; 5= Ifosfamide; 6= Etoposide; 7= Busolfan; 8= Melphalan; 9= L-asparginase; 10= 6 Mercaptopurine; 11= Clofarabine; 12= Rituximab; 13= Cytarabine; 14= Doxorubicin; 15= Carboplatin; 16= Dactinomycin; 17= Gemcitabin; 18= Oxaliplatin; 19= Dacarbazin; 20= Daunorubicin; 21= Fludarabine; 22= Radiation

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Discussion

Due to the rising in the incidence of cancers among children in the last decades in our locality, it is important to understand the factors that influence the outcome and the factors that are associated with diseases like oral mucositis as a result of side effects of different cancer therapies like radiotherapy, chemotherapy, and radio-chemotherapy.

In the current study, there was no correlation between the patient's age and gender with the occurrence of oral mucositis. Our finding is concomitant with the results of several studies that also found no relation between oral mucositis in regards to age and gender in pediatric patients. The main reasons for their conclusion are the lack of standardized methods, different diagnostic criteria, and the description of very few lesions in each survey by Mendonça et al. from Brazil, Majorana et al. from Milan, Italy, and Colaci et al. from Rome, Italy respectively.[5-7] Meanwhile, the reason for the present study is the lack of epidemiologic data in this area which needs further study. Age and gender are identified as less modifiable risk factors for oral mucositis, i.e., the relationship between them is neglected by Otmani et al. from Pediatric Hemato-Oncology Unit, Children's Hospital of Rabat, Morocco.[8]

From the present study, the frequency of distribution of residency was 47% outside of Sulaymaniyah, while 28% and 25% were from Sulaymaniyah and peripheral areas, respectively. This may give the conclusion that environment and quality of life have an important impact on the symptom's incidence and progression. For example, high industrial zones have more chance of infection. Also, the educational and hygienic level may influence the incidence of oral mucositis in patients with cancer.

The present study found a significant negative correlation between the hemoglobin level and intensity of oral mucositis. The current result is contrary to the result of Mendonça et al. from Brazil, which showed no association between hemoglobin level and mucositis intensity. Although they have not mentioned the cause, their small sample size or multifactorial interventions may be counted as a reason in comparison to our study.[5] The strong relationship between Hb level and oral mucositis severity in our result is due to the pathogenesis of oral mucosa in patients with anemia (Hb<10g/dl), in cancer patients who receive chemotherapy that has an adverse effect on bone marrow, leads to anemia and hemoglobin reduction which results in a reduction of epithelial thickness, increase in the progenitor cell layers, but a decrease in cell's number, loss of normal keratinization and atrophy of oral epithelial cell that sequentially causes oral mucositis.[6,7]

The relationship between WBC count and oral mucositis intensity was insignificant from the current study. Our result is in agrees with Murshid et al. from Saudi Arabia.[9] However, according to Devaraju et al. from India, the leukocyte levels below 2,500/μL increase the risk of oral mucositis.[10] The probable reason for the finding of Devaraju et al. is their different association parameter. Their study included all age groups and was concerned only about one type of tumor, esophageal carcinoma, which may give different conclusions.

The effect of ANC level on oral mucositis severity in this study showed a significant relationship which is in agreement with several studies done by Mendonça et al. from Brazil, Cheng et al. from Chicago, USA, Alani et al. from Baghdad, Iraq, and Kishimoto et al. from Japan.[5,11-13] The possible factors for the link between ANC count and severity of oral mucositis rose from the topical and systemic GM-CSF treatment that reduced duration and severity of oral mucositis by recovering neutrophil counts.[11] Predisposition to mucositis is high in patients with low neutrophil counts (<500 cell/μL) because the incidence of microbial infection increased. Another proposed mechanism

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is that repair of the mucosa is accelerated with the recovery of white cells and neutrophil counts.[12]

The present study found no association between platelet counts and oral mucositis. This disagrees with the results of Mendonça et al. from Brazil and Ye et al. from Sweden, who found a highly significant association.[5,14] Their probable reason for their conclusion was the bleeding related to the thrombocytopenia delays the ulcer healing and increases the severity of oral mucositis. Another mechanism for our contradictory result in comparison to the above studies may belong to the statistical analysis where they used platelet counts (<25000 cells/mm^3) as lower cut off which included a small number of patients. However, we used (<50000 cells/mm^3) that included a larger number of patients. Also, in general, their sample size was smaller than ours, which may narrow the range of patients.

From the present study, the relationship between IL-6 and intensity of oral mucositis was found significant (P = 0.003, rho = 0.314). These results agree with Legert et al. from Sweden and Meirovitz et al. from Jerusalem, Israel.[15,16] Bossi and his colleagues found the most significant expression of IL-6 at the severe stage of oral mucositis (P = 0.001).[17] The presence of IL-6 cytokine in the blood is known but a level higher than 10 pg/ml is abnormal and can lead to chronic inflammation.[18]

IL-6 has an important role in the acute phase response. The increase in IL-6 level in serum during transplantation was expected due to tissue damage and the high frequency of septicemia in the group under study. Patients are often infected during transplantation, which may induce systemic inflammation.[19]

This study was unable to find a correlation between IL- 1β and the intensity of oral mucositis (P = 0.706, rho = -0.041). This result is supported by Meirovitz et al. from Jerusalem, Israel.[16] Although there are some studies by Bossi et al. from Milan, Italy, and Curra et al. from Brazil, in contrast with current results, which showed an elevated level of IL-1β.[17,19] Levels in their study group could be elevated due to the impaired immune response. It has been demonstrated that patients with an impaired immune system without the periodontal disease have higher levels of pro- and anti-inflammatory cytokines.

Regarding the level of TNF-β in the serum of participants with oral mucositis, the current study found an insignificant relationship between the intensity of oral mucositis and TNF-β level. During the acute phase of the inflammatory response, the TNF-β is released more than in later phases. This may be a reason for the higher number of cases with abnormal TNF - β out of level having stage one and two of oral mucositis. Studies which measure and relate TNF- β with mucositis are very limited. The same result was found in the present study for TNF-α level in oral mucositis, which showed an insignificant relationship between TNF-α level and intensity of oral mucositis. This result agrees with the results of Meirovitz from Jerusalem, Israel.[16] Pro-inflammatory cytokines such as TNF and IL-1β are expressed within the oral mucosa in patients developing mucositis after receiving radiotherapy for head and neck cancer.[20] Two studies by Bossi et al. from Milan, Italy, and Curra et al. from Brazil found a significant correlation between oral mucositis and TNF- α. The contradictory results of the aforementioned studies from our studies are probably due to the larger involvement of healthy volunteers, other types of malignancy, sample size, and enrollment of the control group.[17,19]

Up to 80% of children undergoing chemotherapy will experience some degree of mucositis, although the incidence of oral mucositis differs according to the type of cancer and treatment regimen.[14,21] Children with hematologic malignancies experience mucositis more frequently than those with solid tumors.[22] Analysis from the present

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study data showed no relation between type of hematological cancer and severity of oral mucositis. The same result concomitant to ours was found by Kishimoto and his colleagues in Japan.[13]

The relationship between the severity of oral mucositis and solid tumor cancer in the present study's result showed a significant difference (P = 0.035, rho = 0.095), which is probably due to the use of aggressive chemotherapy. Its worth mentioning that another reason belongs to chemotherapy is radiation which is a part of treatment in most of the onco-pediatric protocols. Out of the total cases of solid tumors, there were seven cases of neuroblastoma who had undergone bone marrow transplantation during study participation. They have taken busulphan (as part of the conditioning regimen for BMT), which leads to mucositis.

From the present study, methotrexate alone or in a combination course showed more advanced oral mucositis than other chemotherapy. The most common drugs used for treating neoplasms in children and adolescents are: vincristine, paclitaxel, cytarabine, doxorubicin, 5-fluorouracil, cyclophosphamide, cisplatin, and methotrexate; the last four are most commonly associated with the development of changes in the oral mucosa.[19] From the result of the present study, the protocol regimen of etoposide, ifosfamide, and carboplatin showed 11% of oral mucositis out of all other protocols. The reason belongs to the type of combinations of the chemotherapies.

Conclusion

Oral mucositis is a very common devastating adverse effect of chemotherapy and radiation in cancer patients, including pediatrics. This study showed a significant correlation between the intensity of oral mucositis and neutropenia, between the intensity of oral mucositis and low Hb level, between IL-6 level and the intensity of oral mucositis, and the intensity of oral mucositisa with the type of non-hematological cancer. Methotrexate is the most alone chemotherapeutic agent that causes oral mucositis from the included protocols. The combination of etoposide, ifosfamide, and carboplatin showed the most aggressive regimen compared to other used regimens. Correlation between age, gender, WBC count, IL-1beta, TNF alpha, TNF beta, platelet count, type of hematological malignancy, and past history with the intensity of the oral mucositis did not show a significant result.

A larger sample size is recommended in different types of involved pediatric cancers. Also, further types of cytokines are suggested to be studied like interleukin (IL)-1b, IL-1ra, IL-2, IL-4, IL-5, IL-7, IL-8, IL -9, IL-10, IL-12, IL-13, IL-15, IL-17, eotaxin, fibroblast growth factor (FGF) basic, and granulocyte-colony stimulating factor. This will help identify which cytokines' abnormal levels are significantly associated with increased severity of oral mucositis to be used as a marker for severity of oral mucositis. It is recommended to advise the parent regarding signs and symptoms of oral mucositis during the first appearance to decrease the rate of late admission. It is recommended to include a control group and analyze the differences between control and patient groups to have more accurate findings. The current results were from single-center, so it is suggested to involve patients from multi-central data.

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Competing interests

None declared.

References

1. Scully C. Red and purple lesions: Desquamative gingivitis, mucositis In: Scully C, Almeida O, Bagan J, Dios P, Taylor A. Oral Medicine and Pathology at a Glance. 1st ed. Edinburgh: Wiley-Blackwell; 201. P. 128–30.
2. Neville B, Douglas D, Allen G, Chi A. Differential diagnosis of oral and maxillofacial diseases. In: Neville B, Douglas D, Allen G, Chi A. Oral and Maxillofacial Pathology. 4thed. New York: Saunder Elsevier; 2015. P. 267–70.

3. Jeffrey M, Jonathan D. Supportive Care of Patients with Cancer In: Lanzkowsky P, Jeffrey M, Jonathan D. Lanzkowsky's Manual of Pediatric Hematology and Oncology. 6thed. New York: Elsevier; 2016. P. 633–4.
4. Kline N. Leukemia In: Tomlinson D, Kline N, Nancy E. Pediatric Oncology Nursing. 2nd ed. Berlin: Springer; 2010. P. 354–8.
5. Mendonça R, Araújo M, Levy C, Morari J, Silva R, Yunes J, et al. Oral mucositis in pediatric acute lymphoblastic leukemia patients: Evaluation of microbiological and hematological factors. Pediatr Hematol Oncol. 2015; 32(5):322–30. https://doi.org/10.3109/08880018.2015.1034819.
6. Majorana A, Bardellini E, Flocchini P, Amadori F, Conti G, Campus G. Oral mucosal lesions in children from 0 to 12 years old: Ten years' experience. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology. 2010; 110(1):13–8. https://doi.org/10.1016/j.tripleo.2010.02.025.
7. Colaci R, Authors O, Luca G. Most common oral mucosal lesions in children: Prevalence and differential diagnosis. Webmed Central Dent. 2013; 4(12):5–10. https://doi.org/10.9754/journal.wmc.2013.004483.
8. Otmani N. Oral and maxillofacial side effects of radiation therapy on children. J Can Dent Assoc. 2007; 73(3):257–61.
9. Murshid E, Azizrahman T, Aljohar T. Oral mucositis in leukemic Saudi children following chemotherapy. The Saudi Journal of Dental Research. 2017; 8(1–2):79–85. https://doi.org/10.1016/j.sjdr.2016.10.004.
10. Devaraju C, Lokanatha D, Bapsy P. Risk scoring for predicting mucositis in Indian patients with esophageal carcinoma receiving concurrent chemoradiotherapy. Gastrointest Cancer Res. 2009; 3(1):4–6.
11. Cheng K, Lee V, Li C, Goggins W, Thompson D, Yuen H, et al. Incidence and risk factors of oral mucositis in paediatric and adolescent patients undergoing chemotherapy. Oral Oncol. 2011; 47(3):153–62. https://doi.org/10.1016/j.oraloncology.2010.11.019.
12. Alani S, Hassan G, Hameed S. Oral mucositis in children suffering from acute lymphoblastic leukaemia. Iraqi Dent J. 2014; 36(1):30–3. https://doi.org/10.26477/idj.v36i1.7.
13. Kishimoto M, Akashi M, Tsuji K, Kusumoto J, Furudoi S, Shibuya Y, et al. Intensity and duration of neutropenia relates to the development of oral mucositis but not odontogenic infection during chemotherapy for hematological malignancy. PLoS One. 2017; 12(7):1–11. https://doi.org/10.1371/journal.pone.0182021.
14. Ye Y, Carlsson G, Agholme M, Wilson J, Roos A, Henriques B, et al. Oral bacterial community dynamics in pediatric patients with malignancies in relation to chemotherapy-related oral mucositis: A prospective study. Clin Microbiol Infect. 2013; 19(12):E559–67. https://doi.org/10.1111/1469-0691.12287.
15. Legert K, Tsilingaridis G, Remberger M, Ringdèn O, Heimdahl A, Yucel-Lindberg T, et al. The relationship between oral mucositis and levels of pro-inflammatory cytokines in serum and in gingival crevicular fluid in allogeneic stem cell recipients. Support Care Cancer. 2015; 23(6):1749–57. https://doi.org/10.1007/s00520-014-2538-z.
16. Meirovitz A, Kuten M, Billan S, Abdah-Bortnyak R, Sharon A, Peretz T, et al. Cytokines levels, severity of acute mucositis and the need of PEG tube installation during chemo-radiation for head and neck cancer - A prospective pilot study. Radiat Oncol. 2010; 5(1):2–8. https://doi.org/10.1186/1748-717X-5-16.
17. Bossi P, Bergamini C, Miceli R, Cova A, Orlandi E, Resteghini C, et al. Salivary cytokine levels and oral mucositis in head and neck cancer patients treated with chemotherapy and radiation therapy. Int J Radiat Oncol Biol Phys. 2016; 96(5):959–66. https://doi.org/10.1016/j.ijrobp.2016.08.047.
18. Xanthinaki A, Nicolatou-Galitis O, Athanassiadou P, Gonidi M, Kouloulias V, Sotiropoulou-Lontou A, et al. Apoptotic and inflammation markers in oral mucositis in head and neck cancer patients receiving radiotherapy: Preliminary report. Support Care Cancer. 2008; 16(9):1025–33. https://doi.org/10.1007/s00520-007-0379-8.
19. Curra M, Martins MAT, Lauxen IS, Pellicioli ACA, Sant'AnaFilho M, Pavesi VCS, et al. Effect of topical chamomile on immunohistochemical levels of IL-1β and TNF-α in 5-fluorouracil-induced oral mucositis in hamsters. Cancer Chemother Pharmacol 2013; 71(2):293–9. https://doi.org/10.1007/s00280-012-2013-9.
20. Ribeiro I, Valença A, Bonan P. Treatment of severe oral mucositis in a pediatric patient undergoing chemotherapy. RGO - Rev Gaúcha Odontol. 2015; 63(4):467–71. https://doi.org/10.1590/1981-86372015000300014300 7.
21. Cleverson P, Laurindo S, Eduardo M, Roberta Z, Juliana S. Clinical assessment of oral mucositis and candidiasis compare to chemotherapic nadir in transplanted patients. Braz Oral Res. 2014; 28(1):1–7. https://doi.org/10.1590/1807-3107bor-2014.vol28.0050.
22. Suresh A, Varma P, Sinha S, Deepika S, Raman R, Srinivasan M, et al. Risk-scoring system for predicting mucositis in patients of head and neck cancer receiving concurrent chemoradiotherapy. J Cancer Res Ther. 2010; 6(4):448. https://doi.org/10.4103/0973-1482.77100.