Advanced Medical Journal, Vol.10, No.2, P.134-141,2025 https://doi.org/10.56056/amj.2025.352

Oral manifestations of Chemotherapy-Induced Neutropenia in adult patients

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Abstract

Background and Objective: Cancer has become one of the most significant public health issues in recent years, of which chemotherapy is one of the most commonly used therapies. It has a high potential for precipitating oral mucosal damage by reducing absolute neutrophil counts and increasing the risk of life-threatening infections. The objective of this study was to evaluate the association between the incidence of oral complications and chemotherapy-induced neutropenia in adult patients.

Methods: This cross-sectional study, conducted at Hiwa Specialized Oncology Hospital in Sulaimani city from December 2022 to May 2023. The study enrolled 100 neutropenic cancer patients treated with chemotherapy. All participants were referred for routine complete blood count investigation, including white blood cells and neutrophils, to evaluate the neutropenic state of patients and calculate the absolute neutrophil count. The oral cavity was examined, and oral manifestations including any new lesions, mucosal changes, infections, and symptoms were recorded.

Results: Studied sample included (53%) males and (47%) females**.** The majority of patients were aged between 31 and 69 years. Acute leukemia was the most frequent type of cancer (36%). Oral ulcers, were the most frequent oral manifestation, detected in 52 patients and (21.31%) of all oral manifestations. There was a significant association between the absolute neutrophil count, and most of the oral manifestations among the participants (p-value< 0.022).

Conclusions: Oral manifestation observed in chemotherapy-treated cancer patients is directly associated with the level of neutrophil counts, especially oral ulcer, candidiasis, exfoliative cheilitis, and taste disturbance.

Keywords: Cancer, Chemotherapy, Oral complications, Neutropenia

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Introduction

Chemotherapy-induced neutropenia (CIN) is a major and potentially fatal complication in myelosuppressive chemotherapy, in which the absolute neutrophil count (ANC) in peripheral blood is < 2,000 µL. This may affect treatment plans, resulting in unfavorable disease control and leading to decreased response and survival rates. In addition, it usually ends in severe infections, life-threatening morbidity, and even mortality .[1] Neutropenia is classified into four grades: Grade 1 with an ANC of 1,500–2,000 µL, Grade 2 with an ANC of 1,000–1,500 µL, Grade 3 with an ANC of 500–1,000 µL, and Grade 4 with an ANC < 500 µL according to the grading system introduced by the NIC-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5.0).[1]The oral cavity is extremely susceptible to direct and indirect toxic effects of cancer chemotherapy and the defense mechanism of the mouth is severely compromised by the cytotoxic effect of chemotherapy both physically and immunologically, with the possibility of an overall shift in oral microflora.[2,3] In addition, through inflamed periodontal pockets and the epithelial lining of mucous membranes, these oral microorganisms and inflammatory products may transfer into the circulation and disseminate systemically.[4,5] Acute oral complications include mucositis, infection, saliva and neurosensory changes, oral and dental infection, and risk of dental disease and necrosis of the jaw bones. These complications impact the quality of life.[6]A remarkable toxicity of chemotherapy and radiation of the head and neck in cancer patients is oral mucositis (OM). It's an extremely distressful ulceration of the oral cavity and often necessitates the use of systemic analgesics for pain relief, which adversely affects oral hygiene, diet, nutrition, and the overall quality of life.[7]Saliva is crucial in preserving a stable oral environment as it contains many different qualities of peptides and proteins. These include antibacterial, antifungal, and antiviral functions and remineralization, lubrication, buffering, and digestion properties.[8,9] Patients may develop hyposalivation (xerostomia) as a result of cytotoxic chemotherapy, which in turn may contribute to the imbalance in bacterial composition, leading to an increase in the occurrence and severity of complications, including OM, oral mucosal infections, and dental caries.[10] These complications often have long-term detrimental impacts on quality of life, resulting in functional impairment and debilitating morbidity.[11]Moreover, approximately 50% of patients receiving chemotherapy complain of a distressing alteration in taste (dysgeusia) or a reduction in taste sensation (hypogeusia). Taste changes may range from food tasting like cardboard or metal to salty, sweet, sour, or bitter or having no taste. However, this symptom is usually reversible.[12]Furthermore, patients receiving chemotherapy may have oral mucosal infection, resulting in oral ulceration caused mainly by Herpes Simplex Virus (HSV) and Epstein-Barr Virus (EBV). Additionally, the periodontal pocket and salivary gland form the main mechanism for transmitting cytomegalovirus that can be shed through gingival crevicular fluid .[13–15]Moreover, normal oral flora such as Candida albicans, Candida tropicalis, Candida krusei Candida dubliniensis, and other commensal oral yeasts may overgrow and cause oral candidiasis, especially pseudomembranous and erythematous types of which neutropenia, hyposalivation, mucosal impairment, suppressed immunity, use of immunosuppressive and antibiotics drugs are risk factors.[16]Finally, osteonecrosis of the jaw can result from bisphosphonates and other newer drugs used against bone metastases of some types of cancer, such as

https://doi.org/10.56056/amj.2025.352

breast cancer. These drugs affect the function of osteoclasts and osteoblasts and cause osteonecrosis of the jaws.[16,17,18]This study was designed to focus on the most frequent oral-dental complications in chemotherapy-induced neutropenic patients and the correlation of these complications with the level of the absolute neutrophil count.

Patients and methods

This cross-sectional study comprised 100 hospitalized adult cancer patients with different types of cancer, treated by chemotherapy, who were neutropenic. They were hospitalized in Hiwa Specialized Oncology Hospital in Sulaimani city. The study was approved by the Kurdistan Board of Medical Specialties Ethics Committee and carried out from December 2022 to June 2023. Permission was obtained from the hospital to examine the patients, and informed consent was received from all participants. Demographic data (age and sex) and medical information, including the type of cancer and chemotherapy treatment, leukocyte count, and other systemic conditions of the patients, were obtained from the hospital database. Adult neutropenic patients (absolute neutrophil count (ANC) below 1.5 × 109/ µL (1500/ µL), aged 18 years old and above were incorporated in the study. Patients with uncontrolled systemic diseases were excluded. The participants were classified into five age groups (18-30), (31-43), (44-56), (57-69) and (70-85). A new complete blood count (CBC) was performed to evaluate the absolute neutrophil count, and the severity of neutropenia was calculated as follows: NC = white blood cells (µL) x percent (polymorphonuclear cells + bands)/100.The ANC is staged as mild (1000 to 1500/µL), moderate (500 to 999/µL), and severe (200 to 499/µL), while an ANC of (<200/µL) is considered as very severe. Data was tabulated in an Excel worksheet, and the SPSS software package (version 27) was used for statistical analysis. Data are presented in tables as frequency and percentage distributions. Differences among studied parameters were tested by Chi-square and t-test. A P-value less than 0.05 was considered statistically significant.

Results

Studied sample enrolled 47 females and 53 males, and the most commonly affected patients were aged between 31 and 69 years. Acute leukemia (36%) and lymphoma (28%) were among the most common types of enrolled cancer Table (1). Males presented with slightly more oral manifestations (53%) than females (47%), Table (1).

Table (1): Frequency distribution of clinical parameters of the studied group

		No.	%
Gender	Male	53	53.0
	Female	47	47.0
Age	18_30	14	14.0
	31-43	23	23.0
	44_56	22	22.0
	57_69	23	23.0
	70-85	18	18.0
Type of cancer	Acute leukemia	36	36.0
	Lymphoma	28	28.0
	Myelodysplastic syndrome	17	17.0
	Plasma cell dyscrasia	6	6.0
	Aplastic anaemia	6	6.0
	Others	4	4.0
	Myeloproliferative neoplasm	1	1.0
	Solid tumor	1	1.0
	Acute leukemia (unspecific)	1	1.0

The frequency distribution of oral manifestations among cancer patients were grouped into seven clinical signs and symptoms. Macules (2.46%) and gingivitis (2.46%) were the least observed manifestation. Mucosal infections (13.87%) were predominated by candidiasis, and odontogenic infection accounted for (8.6%), Table (2). On the other hand, oral ulceration (21.31%), exfoliative, cheilitis (18.44%), and taste disturbance (17.21%) were the most commonly reported clinical findings among those patients Table (2) and Figure (1).

https://doi.org/10.56056/amj.2025.352

Table (2): The frequency of different oral manifestations among cancer patients

Oral findings		Total		Male 53		Female 47		P value
		No.	%	No.	%	No.	%	
Ulcer (21.31%)		52	21.31	31	58.49	21	44.68	0.16
Macules (n=6, 2.46%)	Purpura	1	0.41	0	0.00	1	2.13	*
	Petechia	5	2.05	2	3.77	3	6.38	0.65
Mucosal infection (n=34, 13.87%)	Abscess	1	0.41	0	0.00	1	2.13	*
	Candidiasis	27	11	15	28.30	12	25.53	0.56
	Herpes simples	6	2.46	1	1.89	5	10.64	0.1
Odontogenic infection		21	8.6	11	20.75	10	21.28	0.82
Gingivitis (n=6, 2.46%)	ANUG	1	0.41	0	0.00	1	2.13	*
	Bleeding gum	5	2.05	2	3.77	3	6.38	0.65
Cheilitis (n=64 26.23%)	Exfoliative cheilitis	45	18.44	28	52.83	17	36.17	0.1
	Angular cheilitis	19	7.79	12	22.64	7	14.89	0.25
Symptoms (n=61, 25%)	Taste disturbance	42	17.21	21	39.62	21	44.68	1
	Dry mouth	19	7.79	9	16.98	10	21.28	0.81
Age Mean ± SD		50.32±17.32		48.72±17.8		52.13±16.76		0.32

ANUG=Acute necrotizing ulcerative gingivitis

*=Not subjected to statistical analysis

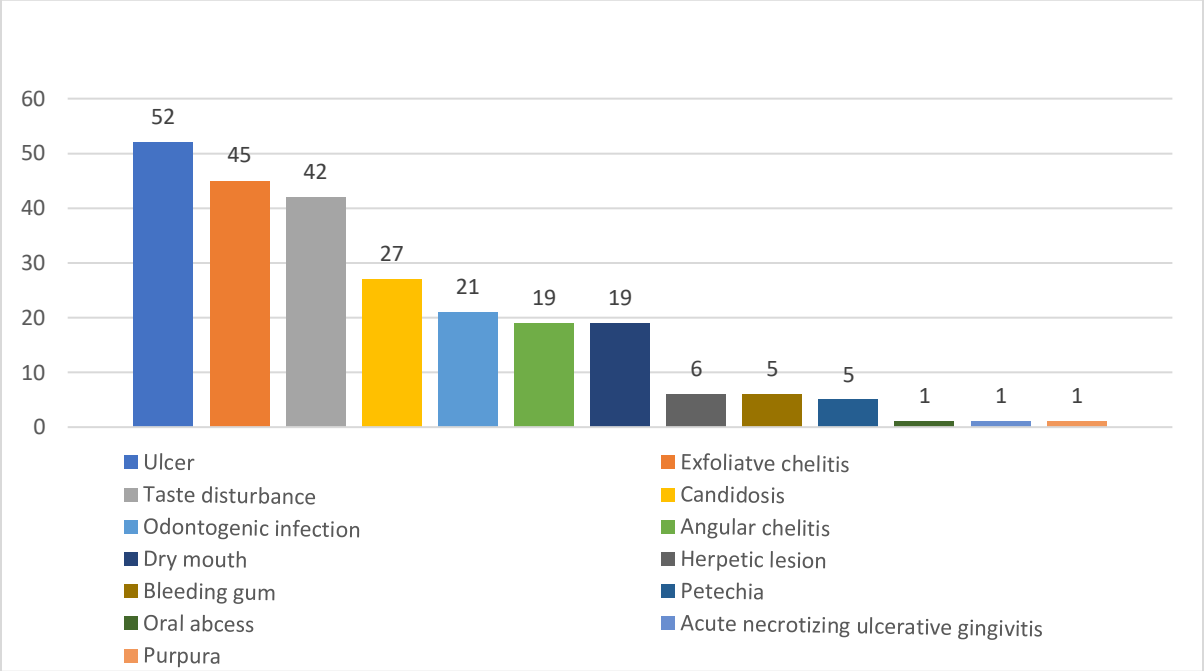

Figure (1): Frequency distribution of the oral manifestation in cancer patients with neutropenia

The absolute neutrophil count ANC was directly associated with several oral manifestations and was significantly higher in patients with decreased ANC. These oral manifestations were odontogenic infection, oral ulcer, candidiasis, gingivitis, dry mouth, taste disturbance, exfoliative cheilitis, and angular cheilitis Table (3). There were no significant association of oral manifestations with age groups. Table (3).

https://doi.org/10.56056/amj.2025.352

Table (3): The association of oral manifestation with age and ANC

Oral Manifestation	ANC	No.	P-value	Age group	No	p value
Petechia	Mild	1	0.819	18_30	0	0.819
	Moderate	2		31-43	2	
	Severe	0		44_56	0	
	Very severe	2		57_69	2	
	Total	5		70-85	1	
Bleeding gum	Mild	0	*	18_30	0	0.819
	Moderate	3		31-43	2	
	Severe	0		44_56	2	
	Very severe	2		57_69	1	
	Total	5		70-85	0	
Candidiasis	Mild	2	0.022	18_30	4	0.722
	Moderate	5		31-43	6	
	Severe	7		44_56	4	
	Very severe	13		57_69	8	
	Total	27		70-85	5	
Herpetic lesion	Mild	0	*	18_30	2	0.881
	Moderate	0		31-43	1	
	Severe	2		44_56	0	
	Very severe	4		57_69	2	
	Total	6		70-85	1	
Odontogenic infection	Mild	0	0.001	18_30	5	0.955
	Moderate	2		31-43	5	
	Severe	4		44_56	4	
	Very severe	15		57_69	4	
	Total	21		70-85	3	
Exfoliative cheilitis	Mild	2	0.002	18_30	7	0.655
	Moderate	12		31-43	11	
	Severe	11		44_56	8	
	Very severe	20		57_69	12	
	Total	45		70-85	7	
Angular Chelitis	Mild	1	0.005	18_30	4	0.498
	Moderate	1		31-43	6	
	Severe	7		44_56	1	
	Very severe	10		57_69	4	
	Total	19		70-85	4	
Oral ulcer	Mild	1	<0.001	18_30	7	0.496
	Moderate	11		31-43	14	
	Severe	14		44_56	9	
	Very severe	26		57_69	13	
	Total	52		70-85	9	
Dry mouth	Mild	0	0.368	18_30	2	0.678
	Moderate	6		31-43	4	
	Severe	4		44_56	3	
	Very severe	9		57_69	6	
	Total	19		70-85	4	
Taste Disturbance	Mild	2	0.001	18_30	6	0.351
	Moderate	9		31-43	10	
	Severe	11		44_56	6	
	Very severe	20		57_69	13	
	Total	42		70-85	7	

*Not subjected to statistical analysis.

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Discussion

Chemotherapeutic drugs are associated with a broad spectrum of hematologic toxicities that include anemia, leukopenia, neutropenia, and thrombocytopenia.[19] A common complication of chemotherapy is neutropenia, which occurs when the myelosuppressive chemotherapeutic treatment reduces absolute neutrophil count.[20, 21] Profound neutropenia occurs when ANC is < 100 cells/µL, while the risk of life-threatening infection develops as the neutrophil count falls below 500 cells//µL and is greater in those with prolonged duration of neutropenia (>7 days).[22] According to above results, acute leukemia (36%) and lymphoma (28%) were among the most common types of diagnosed cancer. This finding supports the study by Quispe et al.,[23] which illustrated that oral manifestations were present principally in acute myeloid leukemia (72.72%) followed by acute lymphoid leukemia (18.18%). In the current study, oral ulceration was the most frequently observed manifestation, followed by exfoliative cheilitis and taste disturbance. These ulcers caused pain and discomfort for the patients. The exfoliative cheilitis, on the other hand, caused pain and bleeding in addition to esthetic problems, while the taste disturbance posed problems in partial or complete loss of taste, yet others complained of a metallic taste. Although the difference was insignificant, this finding is comparable with two previous studies,[19, 20] in which oral ulceration (mucositis) was the most frequent finding. However, their studies were conducted on children. It also agrees with the Rezazadeh et al. result,[24] who concluded that 46.2% of patients reported oral mucositis and 30.8% reported a change in taste sensation, of which 12% had lost their sense of taste completely. This finding could be attributed to the fact that oral tissues are extremely sensitive to the toxic effects of chemotherapeutic agents.[25]Concerning absolute neutrophil count, the present study showed a statistically significant association with some oral manifestations encountered in the patients, such as oral ulcer, angular cheilitis, exfoliative cheilitis, and taste disturbance. This finding aligns with Williams and Martin's study,[26] which reported significant association of low neutrophil counts with oral ulceration. This increase in oral ulceration could be due to bacterial infection because of decreased immune system. Patients with decreased neutrophil count undergoing chemotherapy tend to have higher rate of bacteria and decreased level of salivary IgA.[27, 28]

Conclusion

Chemotherapeutic agents are still the treatment of choice for malignant diseases. The toxic effects of these agents lead to severe infection in the oral cavity. These chemotherapeutic agents also affect the level of neutrophil, which is directly related to the development of oro-dental complications. Among these oral manifestations of chemotherapy-induced neutropenia are oral ulceration, exfoliative and angular cheilitis, dry mouth, and taste disturbance.

Conflict of interest

No conflict of interest was proclaimed.

Acknowledgment

The author like to thank Hiwa Specialized Oncology Hospital cooperative staff and their corporation for performing tests and reaching data when necessary.

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