ORIGINAL ARTICLE

Frequency of Oral Mucositis in Patients with Chemotherapy Induced Febrile Neutropenia

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Abstract

Background: During a period of severe immunosuppression, infections associated with oral mucositis can result in potentially fatal systemic sepsis. One major side effect for patients receiving chemotherapy is febrile neutropenia.

Objective: To determine the frequency of oral mucositis in cancer patients having chemotherapy induced febrile neutropenia.

Material and Methods: A total of 139 patients were involved in this research study. Every cancer patient receiving chemotherapy was evaluated for oral mucositis and febrile neutropenia when they complained of fever and dyspnea. Upon a new complete blood count, neutropenia was observed. The oral health evaluation instrument was used to evaluate oral hygiene. After calculating descriptive statistics, the Chi-Square test was used for association and stratification was done. P-value less than 0.05 is considered as significant.

Results: The mean age was 47.45±12.35 years. There were 31.7% male and 68.3% female patients. The most common primary cancer was breast cancer (53.2%). With regards to disease stage: 47.5% had stage IV disease. The median number of chemotherapy cycles received was 4 (range 1-24). The pancultures were found positive in 12.2% cases. 97.1% received oral care daily and 85.6% had oral mucositis. It was also noted that 98.6% patients had healthy dentures, 72.7% patients had healthy saliva and 44.6% patients had healthy tongues. A significant association of oral mucositis was observed with smoking (p 0.043), stage of cancer (p 0.001) and type of chemotherapy (p 0.006).

Conclusion: Our study showed that the incidence of oral mucositis is 85.6% in patients receiving chemotherapy. Smoking, advanced-stage cancer and a combination chemotherapy were associated with a higher incidence of oral mucositis.

Keywords: *Oral mucositis, cancer, chemotherapy, febrile neutropenia.*

INTRODUCTION

For most malignancies, chemotherapy (CT) represents a significant therapeutic option [1]. In the treatment of some solid tumors and hematological malignancies, chemotherapeutic drugs continue to be essential despite advancements in oncology and anti-cancer treatments including immuno-oncology and targeted medicines [2, 3]. Adverse effects from chemotherapy are common and have a significant impact on morbidity and death [4].

The bone marrow is suppressed by chemotherapy. As a result, the bone marrow produces fewer neutrophils, white blood cells (WBC), platelets, and red blood cells, which increases an individual's susceptibility to infections. A febrile neutropenic state can result from a decrease in neutrophil counts during fever [5]. A decrease in neutrophil counts is the hallmark of chemotherapy-induced neutropenia, which typically happens seven to twelve days after cancer treatment [6]. One of the main causes of chemotherapy dosage decreases or delays is febrile neutropenia (FN). This change in dosage intensity may affect the effectiveness of the treatment, often resulting in hospital stays with high mortality from complications connected to infections [3]. Moreover, FN is associated with significant expenses because of the heightened usage of antibiotics and unanticipated hospital stays [7, 8].

Chemotherapy aims to specifically target and stop the division of cells that divide quickly. They are unable to distinguish between malignancy and normal cells, such as those in the oral mucosa and bone marrow, however. Consequently, following treatment, oral symptoms and side effects are possible [9-11].

Numerous oral symptoms, such as oral ulcers, infections, oral mucositis, and periodontal disease, can result from chemotherapy and neutropenia. These diseases are among the possible oral side effects of chemotherapy and how they affect neutrophil counts [12, 13].

Given that the mucosal membranes are teeming with bacteria, it is not unusual to treat mucositis that manifests as traditional local inflammatory symptoms as an infectious side effect of the chemotherapy that is being administered [14]. Clinicians tend to underreport the occurrence of oral mucositis (OM), which varies from around 15% in cancer patients receiving chemotherapy to over 90% in patients undergoing whole body irradiation (TBI), including those undergoing myeloablative conditioning for hematopoietic cell transplantation (HCT) [15].

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Received: February 02, 2024; Revised: May 29, 2024; Accepted: July 04, 2024
DOI: https://doi.org/10.37184/lnjcc.2789-0112.5.14

Clinical signs of mucositis include pain, erythema, edema, ulcerations in the mouth, discomfort, bowel cramps, nausea, vomiting, and diarrhea in the alimentary tract. Anorexia, weight loss, a worse quality of life, a delay in receiving effective anticancer therapy, and occasionally even an ICU transfer and death are the outcomes of this [15].

The exact function of bacteria in the pathophysiology of mucositis is still up for discussion, as the condition is dynamic, complicated, and convoluted [16]. As previously stated, mucositis is a more complicated process than the simple application of cytotoxic treatment to high mitotic index cells, such as the gastrointestinal tract and oral epithelial cells, which causes apoptosis and a prolonged maturation blockade [14].

An oral examination is usually conducted by the doctor if a patient has FN to determine whether ulcerative OM or mucosal infections are present. Fever, however, can also result from infection and inflammation in other oral areas, such as the salivary glands, the dentition, and the periodontium. This most often refers to persistent illnesses that were asymptomatic before the start of CT [17].

While OM is anticipated to occur in 0-52% of individuals treated with less intense kinds of CT, it is present in most people treated with high-dose CT regimens [18]. Studies on granulocyte stimulating growth factors for the prevention and therapy of OM yield contradictory findings, and the function of neutrophils in the development and resolution of OM remains incompletely understood [19].

The primary aim of the current study was to determine the frequency of oral mucositis in cancer patients having chemotherapy induced febrile neutropenia.

MATERIALS AND METHODS

Our study was a cross-sectional study that was carried out prospectively at the oncology department of Liaquat National Hospital in Karachi, Pakistan, spanning six months from June to December 2021. Approval from the hospital's Research and Ethics Committee was taken before commencement of the study. To acquire consent, participants were educated about the research's goal, as well as the related risks and advantages of the procedure, and they provided written and informed consent before being enrolled in the study.

In our study, we have included 139 patients in total. The sample size was calculated by using the WHO sample size calculator considering 95% confidence level, 8% margin of error, and 64% oral mucositis in chemotherapy induced febrile neutropenia. The non-probability consecutive sampling was used for sample selection. Confidentiality of the participants was maintained throughout the study. Their record number was tagged with other serial number to hide the patient's identity and only principal investigator had the access to original data. The study variables were recorded in the predesigned proforma.

Patients of any gender with ages between 19-75 years having biopsy-proven malignancies, receiving at least 1 cycle of chemotherapy, visited out-patient department or either admitted in-patient via emergency department with a complaint of fever were included. An initial blood workup which included a complete blood count showed neutropenia was done before inclusion in the study. Included patients were assessed for febrile neutropenia and oral mucositis. Patients on myelosuppressive treatments for any other disease other than malignancy, receiving radiation to the head and neck region, other causes of fever related to infection, and had no prior history of oral lesion were not part of the current study.

The diagnosis of cancer was based on the histopathology analysis of the patient's biopsy specimen from any recognized laboratory of the country. Patients were assessed for oral mucositis via clinical examination. During clinical examination, presence of erythematous and ulcerative lesions of the oral mucosa was labeled as oral mucositis. Febrile neutropenia occurred when there was a single reading of oral body temperature *i.e.* more than or equal to 101oF, or a temperature reading more than or equal to 100.40F for at least an hour, with an absolute neutrophilic count (ANC) of not more than 1500 cells/microliter. Absolute Neutrophil Count (ANC) was calculated as 10xWBC count in 1000s x(% PMNs+% bands). Patients were evaluated based on their age, stage of cancer, number and regimen of cycle of chemotherapy. Detailed history and clinical examination were done to assess day of neutropenia with fever, oral hygiene status with co-morbid and smoking status as well. Neutropenia was seen on a fresh complete blood count test. Oral hygiene was assessed by an oral health assessment tool. Data were analyzed using SPSS version 23. Qualitative variables like gender, educational status, smoking status, history of oral cavity surgery, denture, receiving oral care daily, type of cancer, cancer stage, type of chemotherapy, oral health status and oral mucositis were expressed as frequency and percentage. Numerical variables such as age, time since diagnosis of cancer, time since last therapy received, duration of febrile neutropenia were expressed as mean and standard deviation. Effect modifiers such as age, gender, denture, receiving oral care daily, type of cancer, cancer stage, type of chemotherapy, oral health status, time since diagnosis of cancer, time since last therapy received, and duration of febrile neutropenia were addressed through stratification. Post-stratification chi-square test was applied to assess association with oral mucositis. P-value ≤0.05 was taken as statistically significant.

RESULTS

The mean age of the patient cohort was 47.45±12.35 years and 53% of them belonged to age >45years. The mean number of chemotherapy cycles was 7.10±6.78. The mean time since diagnosis of cancer was 9.66±9.59 months. The mean duration of febrile neutropenia was 2.89±1.45 days (**Table 1**).

Table 1: Descriptive statistics of age, cycles, diagnosis and duration.

	Mean±SD	Median (Min-Max)
Age (years)	47.45±12.35	52(22-65)
Number of chemotherapy cycles	7.10±6.78	4(1-24)
Time since diagnosis of cancer (months)	9.66±9.59	6(3-48)
Duration of febrile neutropenia (days)	2.89±1.45	2(1-7)

In this study cohort, there were 31.7% males and 68.3% females. Their educational status was distributed as 1.4% were illiterate, 12.9% had primary education, 15.8% had secondary, 26.6% had intermediate and 43.2% graduates. It was observed that 15.1% patients were smokers, 18% patients had a prior history of oral cavity surgery, 97.1% received oral care daily and 85.6% had oral mucositis. We found that 94.2% patients had healthy lips, 100% patients had healthy oral cleanliness, 97.1% patients had healthy dental pain, 96.4% patients had healthy natural teeth. We also noted that 98.6% patients had healthy dentures, 72.7% patients had healthy saliva and 44.6% patients had a healthy tongue. Their gums and tissues were observed as 41.7% had healthy, 54% had changed and 4.3% had unhealthy gums and tissues (**Table 2**).

Table 2: Frequency distribution of demographic characteristics and clinical findings.

Variables	n(%)
Gender	
Male	44(31.7)
Female	95(68.3)
Education	
Illiterate	2(1.4)
Primary	18(12.9)
Secondary	22(15.8)
Intermediate	37(26.6)
Graduate	60(43.2)
Smoking	
Yes	21(15.1)
No	118(84.9)
Prior History of Oral Cavity Surgery	
Yes	25(18)
No	114(82)
Receiving Oral Care Daily	
Yes	135(97.1)
No	4(2.9)
Oral Mucositis	
Yes	119(85.6)
No	20(14.4)
Status of Lips	
Healthy	131(94.2)
Changes	8(5.8)
Status of Oral Cleanliness	
Healthy	139(100)
Changes	0(0)
Status of Dental Pain	
Healthy	135(97.1)
Changes	4(2.9)
Status of Dental Pain	
Healthy	134(96.4)
Changes	5(3.6)
Status of Dentures	
Healthy	137(98.6)
Changes	2(1.4)
Status of Saliva	
Healthy	101(72.7)
Changes	38(27.3)
Status of Tongue	
Healthy	62(44.6)
Changes	77(55.4)
Status of Gums and Tissues	
Healthy	58(41.7)
Changes	75(54)
Unhealthy	6(4.3)

Regarding primary cancer status, 53.2% patients had breast cancer, 11.5% had hematological cancer, 11.5% had head and neck cancer, 9.4% had prostate cancer, 5.8% had urothelial cancer, 5% had ovarian cancer and 3.6% had soft tissue sarcoma. Most of the patients (90.6%) had combination chemotherapy, 5% patients had platinum chemotherapy while 4.3% had other chemotherapy. The stages of cancer in patients were contributed as 7.9% had stage-2, 5.8% had had stage-2a, 18.7% had stage-2b, 2.9% had stage-3, 2.9% had stage-3b, 11.5% had had stage-3c, 43.2% had stage-4, 4.3% had stage-4b. The pancultures were found positive in 12.2% cases. The isolated organisms in patients were noted as 2.9% had *E. coli*, 2.9% *Klebsiella* / *Pseudomonas*, 2.9% had *Enterobacter* / *E. coli* / *Acenetobacter*, 2.2% had *Providencia rettegri*, and 1.4% had *Pseudomonas* (**Table 3**).

Table 3: Frequency distribution of cancer type, type of chemotherapy, stage, and organisms.

Variables	n(%)
Type of Cancer	
Breast	74(53.2)
Hematological	16(11.5)
Head and neck	16(11.5)
Prostate	13(9.4)
Urothelial	8(5.8)
Ovarian	7(5)
Soft tissue sarcoma	5(3.6)
Regimen/ Type of Chemotherapy	
Platinum	7(5)
Combination	126(90.6)
Others	6(4.3)

Variables	n(%)
Stages of Cancer	
2	11(7.9)
2a	8(5.8)
2b	26(18.7)
3	4(2.9)
3b	4(2.9)
3c	16(11.5)
4	60(43.2)
4b	6(4.3)
unknown	4(2.9)
Pan-Cultures	
Positive	17(12.2)
Negative	122(87.8)
Isolated Organisms	
E. coli	4(2.9)
Klebsiella / *Pseudomonas*	4(2.9)
Enterobacter / *E. coli* / *Acenetobacter*	4(2.9)
Providencia rettegri	3(2.2)
Pseudomonas	2(1.4)
No	122(87.8)

Statistical analysis showed a significant association of oral mucositis with smoking (p=0.043), stage of cancer (p=0.001) and type of chemotherapy (p=0.006). The results showed an insignificant association of oral mucositis with gender (p=0.226), age group (p=0.754), education (p=0.874), prior history of oral cavity surgery (p=0.529), oral care daily (p=1.000), type of cancer (p=0.061), no of chemo cycles (p=0.551), time since diagnosis (p=0.685), duration of febrile neutropenia (p=0.066) and pancultures (p=0.132) (**Table 4**).

Table 4: Association of oral mucositis with demographic, clinical, cancer, and chemotherapy.

Variables	Oral Mucositis		P-value
	Yes (%)	No (%)	
Gender			
Male	40(33.6)	4(20)	0.226**
Female	79(66.4)	16(80)	
Age Group			
≤45 years	55(46.2)	10(50)	0.754**
>45 years	64(53.8)	10(7.2)	
Education			
Illiterate	2(1.7)	0(0)	0.874**
Primary	16(13.4)	2(10)	
Secondary	18(15.1)	4(20)	
Intermediate	33(27.7)	4(20)	
Graduate	50(42)	10(50)	
Smoking			
Yes	21(17.6)	0(0)	0.043*
No	98(82.4)	20(100)	
Prior History of Oral Cavity Surgery			
Yes	23(19.3)	2(10)	0.529**
No	96(80.7)	18(90)	
Receiving Oral Care Daily			
Yes	115(96.6)	20(100)	1.000**
No	4(2.9)	0(0)	
Type of Cancer			
Breast	58(48.7)	16(80)	0.061**
Hematological	12(75)	4(20)	
Head and neck	16(13.4)	0(0)	
Prostate	13(10.9)	0(0)	
Urothelial	8(6.7)	0(0)	
Ovarian	7(5.9)	0(0)	
Soft tissue sarcoma	5(4.2)	0(0)	
Stage of Cancer			
2	11(9.2)	0(0)	0.001*
2a	8(6.7)	0(0)	
2b	23(19.3)	3(15)	
3	4(3.4)	0(0)	
3b	4(3.4)	0(0)	
3c	16(13.4)	0(0)	
4	47(39.5)	13(65)	
4b	6(4.3)	0(0)	
Unknown	0(0)	4(30)	
Type of Chemotherapy			
Platinum	7(5.9)	0(0)	0.006*
Combination	110(92.4)	16(80)	
Others	2(1.7)	4(20)	
No. of Chemotherapy Cycles			
≤5 Cycles	68(57.1)	10(50)	0.551**
>5 Cycles	51(42.9)	10(50)	
Time since Diagnosed			
≤10 months	77(64.7)	12(60)	0.685**
>10 months	42(35.3)	8(40)	
Duration of Febrile Neutropenia			
≤2	68(57.1)	7(35)	0.066**
>2	51(42.9)	13(65)	
Pancultures			
Positive	17(14.3)	0(0)	0.132**
Negative	102(85.7)	20(100)	

Fisher Exact Test was applied.
P-value ≤0.05 is considered as Significant.
* Significant at 0.01 levels.
**Not Significant at 0.05 levels.

DISCUSSION

Chemotherapy can directly harm oral tissues by inhibiting mucosal regeneration, resulting in mucosal atrophy, inflammation, and ulceration [11]. Chemotherapy, being the principal treatment for cancer, can cause the development of oral lesions owing to a variety of reasons. The high pace of cell division in the oral mucosa, the existence of a varied oral flora, and the sensitivity of tissues to harm during normal processes make the oral mucosa especially vulnerable to the effects of chemotherapy [12].

The current study was conducted to determine the frequency of oral mucositis in cancer patients with chemotherapy-induced febrile neutropenia. In our study, most of the patients were aged more than 45 years. The median number of chemotherapy cycles received was 4 (range 1-24). Most of the patients were females. The

mean duration of febrile neutropenia was 2.89 days. It was observed that most of the patients had received oral care daily. The majority of the study participants (85.6%) had oral mucositis. As far as type of cancer is concerned, most of the patients had breast cancer followed by hematological cancer and head and neck cancer. Stage 4 was the most prevalent stage followed by stage 2 b. The results showed a significant association of oral mucositis with smoking, stage of cancer, and type of chemotherapy.

To the best of authors' knowledge, although no research has directly investigated the relationship between neutropenia and oral mucositis, Williams and Martin in 1992 found erythematous alterations in the oral cavity in ten individuals, ranging from mucositis to the appearance of an erythematous ring surrounding ulcers [20].

The findings of a study by Al Beesh *et al.* [9] vary with those of Muhammad and Alzubaidee in 2020, who found a statistically significant relationship between chemotherapy and oral mucositis, with an incidence rate of 46.3% [10]. Study results by Al Beesh *et al.* [9] also contradict those provided by El-Housseiny *et al.* in 2007, who found a statistically significant link between chemotherapy and oral mucositis, with incidence rates of 53.3% [21]. Other investigations, like those done by Subramaniam *et al.* in 2008 and Santilal & Graça in 2019, found oral mucositis in 20.6% and 18.4% of patients, respectively [13]. However, Jena et al in 2022 observed a somewhat lower incidence of chemotherapy-induced oral mucositis, at 10.14% [10].

There is evidence that FN and its possible after-effects may be caused by inflammatory processes in the oral cavity, especially in individuals receiving high-dose CT. Oral infections and OM may also play a role in FN. In particular, OM appears to have a significant role in the development of FN, but there is little information in the literature on other possible oral causes of FN, including mucosal infections, periapical diseases, and pericoronitis [22]. These bouts of bacteremia in non-myelosuppressed people are usually transient. However, bacteremia risk is probably higher in myelosuppressed and other immunocompromised cancer patients because, in addition to having their epithelial barriers violated, these individuals are less able to remove germs from their bloodstream, which increases the risk of infectious consequences. Aspiration pneumonia has been linked to poor oral and dental health in addition to the hematogenous dissemination of oral bacteria and inflammatory mediators [23].

In oncology, the treatment of oral mucositis remains a difficult issue. Reducing the dosage of traditional chemotherapy and prescribing additional therapeutic and preventative medications are only two of the many tactics used to reduce the side effects of cancer treatment [24]. While there is little research on other possible oral causes of febrile neutropenia, such as mucosal infections, periapical diseases, and pericoronitis [25], oral mucositis appears to play a significant role in the development of febrile neutropenia [22].

All of the participants in a research study by Cidon EU [24] who had oral mucositis had good oral hygiene, as this was one of the inclusion criteria. With the current standard of care for oral mucositis, we could only anticipate that patients who began with a grade of 2 or 3 would continue to develop it at the same rate or, most likely, at a greater rate in consecutive cycles, at which point the oral mucositis dosage should be lowered. In actuality, depending on additional contributing variables (such as active smoking, poor dental hygiene, poor oral health, weight loss linked to this condition, the degree and speed of recovery, *etc.*), many patients with oral mucositis grade 2-3 would have had the conventional chemotherapy lowered for the second cycle [24].

In their research study Tanaka Y *et al.* [26] found that breast cancer had the highest incidence of oral mucositis (grade ≥1) following chemotherapy (76.5%), followed by head and neck cancer (66.7%), colorectal cancer (63%), and esophageal cancer (57.8%). In patients receiving DCF, the incidence of grade ≥2 oral mucositis was almost 40%. It is evident that during chemotherapy, oral mucositis occurs more frequently than other non-hematologic toxicities [26].

How to treat possible oral foci of FN is a crucial therapeutic topic. It is generally agreed upon that individuals slated to get high-dose CT should be sent to a dentist for a thorough assessment of their oral and periodontal health and recommended treatment.

Study Limitations

There are certain limitations associated with our study. Firstly, the sample size was relatively small. Secondly, the study's nonrandomized design and single-center experience were also limitations. Because the study was done in an urban setting, it's possible that the findings cannot be applied to broader demographics. Grading of neutropenia and grading of mucositis and its correlation was another limitation of the study, this must be done in future studies to further stratify the association.

CONCLUSION

According to the study's findings, we can conclude that overall, oral mucositis affected the majority (85.6%) of the study population. Regarding cancer types, study findings showed that the majority of the study population had breast cancer. Additionally, the findings demonstrated a strong correlation between smoking, cancer stage, chemotherapy type and oral mucositis.

LIST OF ABBREVIATIONS

CT	Chemotherapy
WBC	White Blood Cells
FN	Febrile Neutropenia
OM	Oral Mucositis

TBI	Total Body Irradiation
HCT	Hematopoietic Cell Transplant
ICU	Intensive Care Unit
WHO	World Health Organization
ANC	Absolute Neutrophilic Count
PMN	Polymorphonuclear
SPSS	Statistical Package for Social Sciences
SD	Standard Deviation
DCF	Docetaxel/Cisplatin/5-FU

ETHICAL APPROVAL

Approval from the hospital's Research and Ethics Committee was taken before commencement of the study (Ref: APP # 0610-2021-LNH-ERC). All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written and informed consent was obtained from the participants of the study.

AVAILABILITY OF DATA

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

AUTHORS' CONTRIBUTION

Dr. Aiman Majid played a significant role in the creation of the original article, spearheading tasks from crafting the synopsis to composing the article and conducting data analysis. Dr. Hafiza Umaima Majid contributed by collecting data and providing assistance with data entry. Additionally, Dr. Shumaila Beg and Dr. Falak Shahab aided in the data collection process and also contributed to the write-up of the article.

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