Oral Complications of Cancer Medication in Hemato-Oncologic Patients

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Abstract

Background: Chemotherapy is used to treat approximately 70% of cancer patients. Oral complications secondary to chemotherapy are recorded in about 80% of hemato−oncologic patients, these complications affect the patients' quality of life and could sometimes be fatal.

Objective: To describe the oral manifestations secondary to chemotherapy medication in hemato-oncologic patients and to determine which of those oral manifestations is more common.

Patients and Methods: A sample of 190 patients presented to Nanakali Hospital for blood-related diseases and cancer in Erbil. The age range of the patients was 3-80 years, (mean 38.35 ± 22.62). Various types of malignancies, types of chemotherapy, and oral manifestation secondary to chemotherapy were recorded.

Results: The most common type of cancer presented was leukemia (37.9%). In patients undergoing chemotherapy, the recorded oral manifestation was mucositis, xerostomia, fungal and viral infection. Mucositis was the most common, being recorded in 46.3% of the subjects.

Conclusion: The results highlight the importance of the presence of a specialist in Oral and Maxillofacial Medicine working in coordination with the medical team to take care of the patients before, during and after chemotherapy. This multidisciplinary team can decrease the frequency of occurrence of oral manifestations, and can even assist in early diagnosis and management of oral lesions in case oral manifestation occurs.

Keywords: Oral manifestation, chemotherapy, hematology-oncology patient, mucositis, fungal infection, xerostomia, viral infection

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Introduction

Cancer, in a comprehensive global terms, is characterized by increased cell proliferation and reduced apoptosis [1]. The incidence of cancer is equivalent to an average increase of 1% every year [2]. Chemotherapy is used to treat about 70 % of cancer patients [3].

Hematology–Oncology patient is defined as a special cancer patient that is characterized by myelo- and immune-suppression related to cancer, chemotherapy or both with an immune-mediated outcome for survival. Those patients are commonly reported with affected blood parameters leading to thrombocytopenia, neutropenia, and anemia [4]. Oral complications secondary to chemotherapy were recorded in about 80 % of Hematology–Oncology patients. These complications were reported as being distorting to the patient's oral functions such as eating, drinking, and speaking [5,6].

Consequently, all these oral lesions and their effects might reduce the patients' quality of life [6]. The issue with chemotherapy medications is that in most cases their action is not selectively targeted to tumor cells. Anticancer drugs affect not only neoplastic cells but also other similarly rapidly dividing normal cells such as bone marrow, hair follicle cells, and the oro-digestive epithelia. Thus, chemotherapy has a narrow borderline between its antitumor effects and toxicity which might, in some cases, be fatal. The chemotherapies have a direct effect by destroying basal cells of the oral mucosal layer and affecting oral mucosal turnover thus causing mucosal ulceration [7].

While indirect toxic effects of chemotherapies result from myelo- or immune suppression and impairment of salivary enzymes [8,9]. It is reported that continuous chemotherapy is associated with a high risk of secondary malignancy due to the damage they cause to the cell's DNA [10]. It is also reported that Hematology–Oncology patients with inadequate DNA repair are more prone to complications of chemotherapy [11]. Since the evolution of chemotherapy in the last century, multiple and continuous efforts have been taking place to improve and analyze their action by combining these agents and lowering their adverse effects [12,13]. In general, chemotherapy may be responsible for many systemic side effects like bone marrow suppression, anemia, hair loss, nausea, and vomiting, etc. Regarding the oral side effects, oral mucositis is reported to be the most common side effect of chemotherapy among Hematology–Oncology patients which presents clinically as a painful inflammatory reaction of oral mucosa with infiltration of the inflammatory cells followed by epithelial ulceration [14]. Previous studies reported that oral side effects were caused by most known traditional chemotherapy drugs like antimetabolites (Fluorouracil, Xeloda, Gemzar), Doxorubicin (Adriamycin), alkylating agents (cyclophosphamide, cisplatin), Bleomycin, Taxanes and Methotrexate [15,16]. Infections are also regarded as common oral complications of chemotherapy. The chemotherapy causes neutropenia thus leading to a higher risk of infections, in addition to fact that the oral cavity is commonly vulnerable to different infections, bacterial, fungal, or viral [17]. The hyposalivation and xerostomia are the result of chemotherapy effects on salivary glands function and are regarded as temporary and reversible effects, however, they can cause discomfort to the patient during speaking and eating, in addition to the impairment of salivary functions such as lubrication, moistening, and antimicrobial properties

[13]. Chemotherapy could change the patient's quality and quantity of saliva. Moreover, the decrease in the amount of IgA and IgG during chemotherapy makes the oral mucosa more prone to trauma and oral mucositis. Other reported oral complications of chemotherapy were lichenoid reactions, dental anomalies, taste changes, bleeding, neurotoxicity, oral hyperpigmentation-melanosis, and Steven-Johnson syndrome [18]. Studies in Iraq detected many oral manifestations after cancer treatment with chemotherapy such as ulceration, dry mouth, bleeding and taste changes [19,20]. Previous studies demonstrated that the magnitude of these side effects depends on a number of risk factors related to the following: firstly, therapy (type, dose, frequency, duration, drug target); secondly, tumor (nature, extent); and lastly the patient (age, malnutrition, gender, pre-existing medical problems, poor oral health, alterations in salivary production and composition, mucosal trauma, poor dental health particularly periodontal disease, use of alcohol and/or tobacco, liver disease, and kidney functional status) [18]. Unfortunately, the registered cancer incidence rates in Iraq and Kurdistan region have increased from 31/100,000 in 1991 to 57/100,000 in 2010 [21]. The high incidence rate of cancer has led to an increased need for chemotherapy agents for treatment and subsequently an increase in the accompanying oral complications. Few studies by Iraqi Clinicians recorded the adverse effects of different categories of chemotherapies [22].

However, there is a scarcity of research discussing this problem in the Kurdistan region. Previous studies exhibited a correlation between anticancer treatments, particularly chemotherapy, and the occurrence of oral complications [24,25,3]. Thus, was the rationale of the present study which aimed to highlight, observe, describe and evaluate the most common oral manifestation secondary to chemotherapy medication in Hematology- Oncology patients.

Patients and Methods

This is a descriptive cross-sectional study conducted in Erbil city-Kurdistan region, Iraq. The study sample was patients presented to Nanakali Hospital for blood diseases and cancer were diagnosed with oncology-hematology cancer, and whom the oncologist and /or hematologist had decided to start on chemotherapy. The study duration was 8 months (1st of June 2019 – 31st of January 2020). A convenient sample of 190 Oncology-Hematology patients was selected after eligibility to inclusion and exclusion criteria. Ethical considerations were applied according to Helsinki Declaration by obtaining approval of the study from the Ethical Committee of Kurdistan Board of Medical Specialities and Nanakali Hospital authorities. Oral informed consent of patients were obtained, in addition to taking into consideration the confidentiality of patients' data with the management of oral lesions accordingly. The inclusion criteria for the selected sample were confirmed diagnosis of Oncology-Haematology cancer; indicated for chemotherapy and the availability of full data and records regardless of age and gender of patients.

The exclusion criteria were diagnosed Oncology-Haematology cancer cases but not

receiving chemotherapy; pregnant women; lactating women; patients treated with surgery or radiotherapy; unconscious patients; lacking full data and/or patients refused to participate. The data was collected directly from patients, other information like chemotherapy protocol and the number of treatment cycles was also collected from the patients and then verified by the patients' records. Patients were categorized into seven age groups (<10 years, 10-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, and ≥60 years), the age range was 3-70 years. Patients' data were registered using a questionnaire form where the following were recorded: patient's age; gender (male or female); systemic diseases (yes or no); types of malignant diseases; protocols of treatment; oral lesions detected before and after chemotherapy. Sialometry was performed, for each patient, to detect hyposalivation. Oral rinse was collected from each patient and sent to Rizagree hospital laboratory for detection of fungal infection. Identification of type of fungal infection was done by Vitek technique which was also conducted in the same laboratory.

All patients were examined and diagnosed by the first investigator, who also recorded and photographed the following oral manifestations:

1.Mucositis: diagnosed via clinical examination whether present or not.

2.Xerostomia: diagnosed through sialometry by evaluating the production of unstimulated saliva. Individuals commonly produce 0.3 ml/min of saliva without stimulation, when secretion is ≤ 0.1ml/min, it is characterized as hyposalivation [3].

3.Fungal infection: diagnosed with the oral rinse technique [23].

4.Viral infection: diagnosed via clinical examination.

The patients were assessed at 2 stages. The first study stage (before or within 3 days of starting chemotherapy), where complete information was taken. Intra orally, the buccal, labial and sulcular mucosa, the dorsum of the tongue, the hard and soft palate, fauces, floor of the mouth, and gingiva were examined by the first investigator for any abnormalities. The oral side effects due to chemotherapy looked for were mucositis, xerostomia, fungal infection and viral infection. The second study stage where follow-up screening was conducted and all the aforementioned parameters in stage one were examined after one week, two weeks and one month after the initiation of chemotherapy in the hematology /oncology ward and at the outpatient clinic, to record any differences and compare the results.

Statistical analysis

The data collected were analyzed statistically by the Statistical Package of Social Sciences software (SPSS-version 22). McNemar-Bowker test was applied for analyzing the categorical data before and after chemotherapy. The level of significance (p-value) was regarded as statistically significant if ≤ 0.05.

Results

The total number of patients was 190. Their mean age ± SD was 38.35 ± 22.62 years, ranging from 3-70 years and the median was 42 years. The highest proportion of the sample (24.2%) was aged ≥ 60 years, and 19.5% of the sample were in the range of 50-

59 years, as presented in Table (1). The table shows also that 61.6% of the sample were females, and 14.7% had systemic diseases. Table 2 shows that the most common type of cancer was leukemia (37.9%), followed by lymphomas (16.8%), and breast cancer (15.3%). The fourth most common type was lung cancer.

Table (1): Distribution of patients according to the age range, gender, and the presence or absence of systemic diseases

	No.	(%)
Age (years)		
< 10	27	(14.2)
10-19	27	(14.2)
20-29	20	(10.5)
30-39	14	(7.4)
40-49	19	(10.0)
50-59	37	(19.5)
≥ 60	46	(24.2)
Gender		
Male	73	(38.4)
Female	117	(61.6)
Systemic disease		
No	162	(85.3)
Yes	28	(14.7)
Total	190	(100.0)

Regarding treatment protocols, the most common was UKALL (United Kingdom Acute Lymphoblastic leukemia) (16.3%), followed by the AML (Acute Myeloid Leukemia) Protocol (Cytosar and Daunorubicin) at 13.2%, and the ACT (Adriamycin – Cyclophosphamide- Taxole) at 10.5%. All protocols are presented in Table (3). Analysis of treatment cycles in Table 4 showed that around one third (32.6%) of the sample had one cycle, 18.9% had two cycles, and 15.3% had three cycles.

Table (2): Distribution of the patients according to the type of malignant diseases they have

Malignancy	No.	(%)
Leukemia (ALL/ AML/APL)	72	37.9
Lymphomas (NHL/ HL)	32	16.8
Breast cancer	29	15.3
Lung cancer	15	7.9
Colorectal cancer	13	6.8
Multiple Myeloma	6	3.2
Hepato-biliary malignancy	5	2.6
Head and neck cancer	5	2.6
Myelodysplastic syndromes	3	1.6
Ewing sarcoma	2	1.1
Germ cell tumor	2	1.1
Prostate cancer	2	1.1
Rhabdo-myosarcoma	1	0.5
Hydatidiform mole	1	0.5
Adrenal tumor	1	0.5
Brain tumor	1	0.5
Total	190	(100.0)

*ALL/AML/APL= Acute lymphoblastic leukemia/acute myeloid leukemia/Acute promyelocytic leukemia; NHL/HL=Non- Hodgkin's lymphoma/ Hodgkin's lymphoma

Table (3): Distribution of the patients according to the treatment protocol used

Protocol	No.	(%)
UKALL (United Kingdom Acute Lymphoblastic Leukemia)	31	(16.3)
Acute Myeloid Leukemia Protocol (cytosar +daunorubicin)	25	(13.2)
ACT (Adriamycin – cyclophosphamide- Taxole)	20	(10.5)
Xelox (Oxaliplatin-Xeloda)/ FOLFOX	13	(6.8)
Cisplatin-Gemzar OR Cisplatin+/-Alimta	11	(5.8)
UKCCSG (United Kingdom Children's Cancer Study Group)	10	(5.3)
Hyper CVAD (Hyper fractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone).	9	(4.7)
R-Chop (Rituximab, Cyclophosphamide, Hydroxydaunorubicin hydrochloride (Doxorubicin hydrochloride), Vincristine (Oncovin) and Prednisone)	9	(4.7)
Taxane+/Gemzar	8	(4.2)
Taxotere-Cisplatin-5fluorouracil OR Taxotere	5	(2.6)
ABVD (doxorubicin hydrochloride (Adriamycin), Bleomycin sulfate, Vinblastine sulfate, and Dacarbazine).	4	(2.1)
Carboplatin+Gemzar+/Zometa	4	(2.1)
Vidaza	3	(1.6)
Daunorubicin	3	(1.6)
VTD (Velcade-Thalidomide-Dexamethasone)	3	(1.6)
Decitabine (Dacogan)	3	(1.6)
DHAP (Dexamethasone, Cytarabine, and Cisplatin)	2	(1.1)
Cisplatin+etoposide	2	(1.1)
Velcade	2	(1.1)
ATRA (All-trans-retinoic acid)	2	(1.1)
Taxotere+Herceptin	2	(1.1)
Pemetrexate-carboplatin	2	(1.1)
Carboplatin+taxotere	2	(1.1)
COP (Cyclophosphamide, Hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], and Prednisone)	2	(1.1)
Cefuximab +Irinotecan	2	(1.1)
Vac-IE (Vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and Cyclophosphamide - Ifosfamide and Etoposide phosphate).	1	(0.5)
Carfilzomib+cyclophosphamide	1	(0.5)
ICE (Ifosfamide, Carboplatin, Etoposide)	1	(0.5)
Carboplatin-Etoposide	1	(0.5)
ESHAP (Etoposide, Methylprednisolone, Cytarabine, Cisplatin)	1	(0.5)
5flurouracil-cyclophosphamide-Taxotere	1	(0.5)
EMA/CO(Etoposide, Methotrexate, Actinomycin, Cyclophosphamide,and Vincristine)	1	(0.5)
Casodex-zoledax	1	(0.5)
FLAGID	1	(0.5)
PCV (procarbazine, CCNU (or lomustine), and vincristine)	1	(0.5)
Cisplatin+Avastin	1	(0.5)
Total	**190**	**(100.0)**

Table (4): Distribution of the patients according to the number of treatment cycles

Cycle	No.	(%)
1	62	(32.6)
2	36	(18.9)
3	29	(15.3)
4	30	(15.8)
5	8	(4.2)
6	8	4.2)
7	6	(3.2)
8	3	(1.6)
10	2	(1.1)
11	1	(0.5)
12	2	(1.1)
13	1	(0.5)
17	2	(1.1)
Total	**190**	**(100.0)**

In Table (5), it is evident that the majority (91.1%) of the patients had no oral manifestations before chemotherapy. However, the single most striking observation to emerge from the data comparison is that after chemotherapy all patients had some form of oral manifestations with around half of them (46.3%) developing mucositis, 24.2% developing fungal infections, 19.5% had xerostomia, and the rest (10.0%) developed viral infections. The difference was significant for all types of oral manifestations between before and after treatment (p < 0.001) Table (5).

Table (5): Distribution of the patients with regard to oral manifestations before and after chemotherapy

	Before Chemotherapy		After Chemotherapy		p
	No.	(%)	No.	(%)	
Oral Manifestations					
None	173	(91.1)	0	(0.0)	
Mucositis	1	(0.5)	88	(46.3)	
Fungal infections	8	(4.2)	46	(24.2)	< 0.001*
Xerostomia	0	(0.0)	37	(19.5)	
Viral infections	8	(4.2)	19	(10.0)	
Total	190	(100.0)	190	(100.0)	

*By McNemar-Bowker Test

Discussion

Modernization and advancement in chemotherapy for treating cancers are hopeful and are declining the mortality rates worldwide. However, these chemotherapies are accompanied by many adverse effects including oral side effects that need specific oral care [24]. This study showed a highly significant increase in the incidence of oral lesions after chemotherapy (p<0.001). These results corroborate the findings of previous work by other researchers such as Al-Kuhla and Al-Aswad study in Iraq [20], Tabari et al

study in Iran [25], and Velten et al study in Brazil [3] all of which revealed a significant increase in the number of oral lesions for cancer patients after receiving their chemotherapy. Many guidelines regarding dental care during chemotherapy were published in order to help the physicians responsible for the management of hematology-oncology patients in providing better care for their patients [26,27]. Despite that, the practice of oral care differs between or within different centers and these differences might be due to discrepancies in oral/dental care service quality, which complicates the incorporation of these guidelines to chemotherapy protocols especially in the absence of harmony between many guidelines [28]. The current study found that after chemotherapy, around half of the patients (46.3%) developed mucositis, 24.2% developed fungal infections, 19.5% developed xerostomia, and the rest (10.0%) developed viral infections. These findings are consistent with results of Murshid et al study in Saudi Arabia [29] and Acharya et al study in India [30] both of which reported that cancer patients were more liable for oral lesions such as oral mucositis, xerostomia, and infections after receiving chemotherapy. A study in Iraq by Atoof et al [19] found that the main oral manifestations of leukemic children under chemotherapy were ulceration, bleeding, dry mouth, ulcerated lips, inability to swallow and mucositis. These differences in symptoms might be attributed to differences in cancer types and chemotherapy protocols between different studies. Oral lesions following chemotherapy were reported

previously to be within a wide range of 12% to 80% among oncology-hematology patients. Oral mucositis was reported among one-third of those patients and it was highlighted that leucopenia, fever, and long duration of chemotherapy were risk factors for oral mucositis [31]. It was stated in previous research that after chemotherapy, the patient's quality and quantity of saliva is altered. When the salivary flow rate decreases, the oral mucosa will become more susceptible to trauma and friction. Subsequently, oral mucositis will develop along with the impairment of salivary functions like lubrication, moistening, and antimicrobial properties [18]. The reduction of saliva can cause a disruption of oral flora, the most common result of this imbalance is an overgrowth of *Candida albicans* [32]. Once the volume of the whole saliva decreases with the concentration of lactoferrin, IgA, salivary proteins, and peptides, liability to fungal infections increases. Drinking a large amount of water in combination with the use of sugar-free sweets and chewing gums were shown to be beneficial in the management of hyposalivation and xerostomia. In more serious situations, pilocarpine can be used [18].

Fungal infections are reported as the main cause of co-morbidity in cancer patients after chemotherapy and that they also potentiate the risk of esophageal candidiasis [32]. These oral lesions might have a very severe manifestation that could interrupt the chemotherapy course [33].

In the present study, the highest prevalence of oral lesions was found in elderly patients

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Table (1). This result accords with the findings of Tabari et al [25], who stated that old age was a common risk factor for oral lesions following chemotherapy. According to Balducci and Exterman [34], patients over 50 years of age develop oral mucositis, due to insufficient DNA repair, which could be a possible explanation of the current results. Conversely, some authors documented that mucositis was more common among younger age patients[35] and that it is possibly due to high cellular turnover [16]. Females in the present study were more than males. This finding coincides with the results reported by Vokurka et al [36] randomized multi-center study in Slovakia which found that female gender was an independent risk factor for oral mucositis among cancer patients treated with chemotherapy. Systemic diseases in the present study were found in (14.7%) of cancer patients with oral lesions. It was reported previously that a history of systemic diseases has an important role in the development of oral lesions during or after chemotherapy [18].

In the current study, the most common oncology-hematology cancers with oral lesions were leukemia, lymphoma, breast cancer, and lung cancer Table (2). These findings are in agreement with the results of the Hassan et al study in Iraq [22] and the Jensen et al study in Denmark [37] which found a higher predominance of oral lesions after chemotherapy of patients with leukemia, lymphoma, breast cancer, and lung cancer.

The most common treatment protocols used for patients in this study were UKALL (United Kingdom Acute Lymphoblastic Leukemia), AML (Acute Myeloid Leukemia) Protocol (Cytosar–Daunorubicin), and the ACT (Adriamycin – Cyclophosphamide-Taxole) protocol as shown in Table (3) which also shows that in agreement with previous studies oral lesions differ in incidence with different chemotherapy protocol, type, and dose [38].

Conclusions

The risk of oral lesions increases following chemotherapy for oncology-hematology patients. Oral mucositis was the prevalent oral lesion after chemotherapy. Thus, the presence of a specialist in Oral and Maxillofacial Medicine working in coordination with the medical team is important to take care of the patient before during and after chemotherapy.

Recommendations

It is recommended to educate the patients about the importance of strictly committing to oral care guidelines parallel to chemotherapy protocols to reduce their oral side effects. The adoption of the aforementioned practices could enhance the patient's quality of life and decrease the urgent need to stop the chemotherapy due to these oral side effects.

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