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ORIGINAL RESEARCH

MATRIX METALLOPROTEINASES AND CYTOKINE EXPRESSION IN CHEMOTHERAPY-INDUCED ORAL MUCOSAL INJURY

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ABSTRACT

Background:Oral complications are common in women using chemotherapy and are commonly attributed to the systemic inflammation and immune silencing. Nevertheless, the biochemical association of particular oral manifestations and inflammatory biomarkers in Iraqi women has not been explicitly determined.

Objective: This research paper was done to examine the relation between oral manifestations (ulcer, stomatitis, and periodontitis) and the serum concentration of interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9), and indoleamine 2, 3-dioxygenase (IDO) in Iraqi women under chemotherapy treatment.

Methods:Eighty-six chemotherapy treated women were utilized and categorized in the presence or the absence of oral manifestations. The concentration of IL-6, MMP-9 and the IDO was measured using serum and statistically analyzed between the affected and unaffected group.

Results: In those with oral ulcers, significantly higher levels of IL-6 (23.5 +- 5.8 vs. 16.7 +- 4.2 pg/mL; p = 0.001), MMP-9 (459.2 +- 68.5 vs. 392.4 +- 70.2 ng/mL; p = 0.004) and IDO (2.88 +- 0.71 vs. 2.41 +- 0.63 U The high-level of IL-6 and MMP-9 were also observed in the women with stomatitis and periodontitis as compared to those who did not have them.

Conclusion: The results imply that IL-6, MMP-9, and IDO are important in the pathogenesis of oral manifestations in Iraqi women who are under chemotherapy. These biomarkers could be the indicators of the overall inflammation of the system caused by cytotoxic treatment and could be used as the signs of early detection and treatment of oral complications during chemotherapy

Keywords: Oral manifestations, IL-6, MMP-9, IDO, Iraqi women, inflammation, Chemotherapy

INTRODUCTION

Mucositis and oral ulcerations represent frequent and debilitating complications following cytotoxic chemotherapy, significantly impacting a patient's quality of life, nutritional status, and treatment continuity. The pathogenesis of these oral lesions is complex and multifactorial, involving direct damage to the basal epithelial cells and a cascade of inflammatory events within the oral mucosa[1].

This inflammatory response is characterized by the upregulation of key biological mediators that drive tissue breakdown and impede healing. Central to this process is the activation of pro-inflammatory cytokines, such as Interleukin-6 (IL-6), which amplifies the local inflammatory signal and contributes to pain and tissue damage[2].

Concurrently, the expression and activity of Matrix Metalloproteinases (MMPs), particularly collagenases and gelatinases, are significantly increased, leading to the degradation of the extracellular matrix and the basement membrane, thereby facilitating ulcer formation[3].

Furthermore, the local immune microenvironment is profoundly altered by enzymes like Indoleamine 2,3-Dioxygenase (IDO), which, through the catabolism of tryptophan, creates an immunosuppressive milieu that may compromise mucosal immune surveillance and repair mechanisms, potentially exacerbating the severity and duration of lesions[4]. Understanding the interplay between IL-6, MMPs, and IDO is crucial for developing targeted strategies to prevent and manage oral complications in patients undergoing chemotherapy. The management of oral complications in patients undergoing chemotherapy remains a significant clinical challenge, particularly in cases of recurrent aphthous ulceration (RAU) that persist or emerge during treatment cycles.

The pathogenesis of these recurrent ulcers extends beyond the direct cytotoxic effects of chemotherapeutic agents and is deeply intertwined with a state of heightened oxidative stress. A critical consequence of this stress is lipid peroxidation, a process where free radicals degrade polyunsaturated fatty acids in cell membranes, leading to the generation of toxic byproducts such as Malondialdehyde (MDA). Elevated levels of MDA serve as a key biochemical marker of cellular damage and are closely linked to the severity of mucosal injury[5].

The study aimed to determine the role of some biomarkers Matrix Metalloproteinase, IL-6 and Indoleamine 2,3-Dioxygenase (IDO) in serumof Iraqi women breast cancer after traetment with chemotherapy.

MATERIALS AND METHODS

Study Population

A total of eighty-six Iraqi women undergoing chemotherapy were enrolled in the present study. All participants were recruited from **Al-Hussein Teaching Hospital** and **Al-Hassan Hospital** in Karbala City, Iraq. Written informed consent was obtained from all patients prior to their inclusion in the study. The study protocol was approved by the institutional ethics committee in accordance with the Declaration from medical college of kerbala university.

Clinical Examination

Each participant underwent a comprehensive oral examination that was performed by a qualified dental specialist. The examination was conducted to identify clinical features associated with chemotherapy-induced oral mucosal injury. The following manifestations were assessed and recorded: the presence of oral ulcerations, mucosal erythema, stomatitis, recurrent aphthous ulcerations, disturbances in taste perception including bitter or sweet sensation, and periodontal inflammation. The severity and distribution of these lesions were carefully documented.

Sample Collection

Peripheral blood samples were obtained from the antecubital vein of each patient under aseptic conditions. Approximately 5 mL of venous blood was collected into EDTA tubes for hematological and biochemical analyses. In addition, whole saliva samples were collected from each patient using the unstimulated drooling method in the early morning hours to minimize circadian variation. The saliva samples were immediately placed on ice and transported to the laboratory for further processing.

Laboratory Investigations

Plasma and saliva samples were centrifuged at 3000 rpm for 15 minutes at 4°C, and the supernatants were aliquoted and stored at −80°C until analysis. The expression levels of matrix metalloproteinases (MMPs) and selected interleukin-1 beta [IL-1β]) were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's protocols.

The activity of indoleamine 2,3-dioxygenase (IDO) was measured from saliva samples using a colorimetric assay, and its concentration was expressed in units per milliliter. To provide a broader assessment of the oxidative and inflammatory milieu, malondialdehyde (MDA) was also measured as an index of lipid peroxidation, and total antioxidant capacity (TAC) was evaluated using spectrophotometric assays.

Statistical Analysis

All data were entered into a computerized database and analyzed using the Statistical Package for the Social Sciences (SPSS, version 27.0). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons between groups were conducted using independent t-tests or one-way analysis of variance (ANOVA), as appropriate. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study cohort included 86 Iraqi women undergoing chemotherapy, with a mean age of 46.8 ± 9.2 years. In terms of age distribution, 22 participants (25.6 %) were younger than 40 years, 34 (39.5 %) were between 40 and 49 years, and 30 (34.9 %) were 50 years or older. Most subjects were married (70/86, 81.4 %), while 16 (18.6 %) were single. Regarding smoking status, 12 (14.0 %) of the women were smokers, and 74 (86.0 %) were non-smokers. Concerning chemotherapy regimens, 28 (32.6 %) received anthracycline-based therapy, 24 (27.9 %) received taxane-based therapy, and 34 (39.5 %) were treated with combined regimens. In the present cohort, a relatively broad age range was covered (mean ≈ 46.8), with about one quarter (25.6 %) younger than 40, about 39.5 % in the 40–49 bracket, and about 34.9 % aged 50 or older. This age distribution is consistent with many studies of adult female cancer populations receiving chemotherapy, where middle age is common. Marital status was heavily skewed toward married participants (81.4 %), which may reflect demographic or social patterns in the local population. Smoking prevalence was relatively low (14.0 %), which is beneficial, considering that tobacco use has been

associated with worse oral mucosal outcomes and impaired healing in mucositis studies.

Table 1. Demographic and Clinical Characteristics of the Study Population (n = 86)

Variable	Categories	n (%)
Age (years)	Mean ± SD = 46.8 ± 9.2	—
Age group (Years)	<40	22 (25.6)
	40–49	34 (39.5)
	≥50	30 (34.9)
Marital status	Married	70 (81.4)
	Single	16 (18.6)
Smoking status	Smoker	12 (14.0)
	Non-smoker	74 (86.0)
Chemotherapy regimen	Anthracycline-based	28 (32.6)
	Taxane-based	24 (27.9)
	Combination	34 (39.5)

Regarding chemotherapy regimens, the largest group (39.5 %) was treated with combination regimens, followed by anthracycline-based (32.6 %) and taxane-based (27.9 %) regimens. This variation is relevant because different chemotherapeutic agents are known to confer different risks of oral mucosal injury (mucositis/ulceration) depending on their cytotoxic profile and mechanisms of action (e.g. antimetabolites, alkylating agents[6], In general oncology settings, approximately 20–40 % of patients undergoing conventional chemotherapy develop some level of oral mucositis[6]. Similarly, on the other hand [7]reported that in women under chemotherapy, about 55 % experienced mucositis in a multicenter cross-sectional study [8]. In more intensive regimens or combined chemo-radiation therapy, rates rise substantially (up to 60 % or more)[9]. In this current sample, although mucositis incidence per se has not yet been tabulated in Table 1, the distribution of risk factors (age, smoking, chemo regimen) suggests a sufficiently heterogeneous sample in which associations with biomarkers and clinical outcomes can be meaningfully explored. The relatively low smoking prevalence might have mitigated one known risk factor for mucosal injury, on the other hand, the use of combination regimens in nearly 40 % of patients suggests that many subjects were exposed to potentially higher mucotoxic risk, which should be taken into account when interpreting biomarker associations [10]

Of the 86 chemotherapy-treated women, various oral conditions were observed (Table). Oral mucosal changes were common: 38 women (44.2 %) developed oral ulcers, 52 (60.5 %) had mucosal redness, and 41 (47.7 %) manifested stomatitis. Recurrent aphthous ulcers occurred in 29 patients (33.7 %). Disturbance in taste (bitter or sweet) was reported by 47 participants (54.7 %). Periodontitis was diagnosed in 35 women (40.7 %).

Table 2. Oral Manifestations in Chemotherapy-Treated Patients

Oral condition	n (%)
Oral ulcer	38 (44.2)
Mucosal redness	52 (60.5)
Stomatitis	41 (47.7)
Recurrent aphthous ulcer	29 (33.7)
Disturbance in taste (bitter/sweet)	47 (54.7)
Periodontitis	35 (40.7)

The present findings indicate a high prevalence of oral mucosal injury among the studied population. Oral ulceration was noted in 44.2 % of patients, mucosal redness (erythema) in 60.5 %, and stomatitis in 47.7 %. These rates are consistent with published estimates indicating that clinical mucositis (including ulceration and erythema) occurs in about 30–40 % of patients treated with conventional chemotherapy, rising under more intensive regimens [11]. Mucosal redness was the most frequent manifestation (60.5 %), possibly representing the earliest and mildest stage of mucosal injury prior to ulceration development. The progression from erythema to ulceration is well described in the mucositis pathogenesis model (initiation, signaling, amplification and ulceration) [12].

Because erythema may precede ulcer formation, its higher prevalence aligns with the notion that not all mucosal irritation culminates in full ulceration. Stomatitis (inflammation of the oral mucosa) was present in nearly half (47.7 %) of participants, reinforcing that generalized mucosal inflammation is a common adverse event in chemotherapy. The observed frequency of recurrent aphthous ulcers (33.7 %) suggests that a subset of patients experience repeated localized ulcerative lesions beyond diffuse mucositis. This recurrent ulceration may reflect individual susceptibility, possibly mediated by inflammatory cytokines, local microbiome, or pre-existing mucosal fragility [12].

Taste disturbance (dysgeusia) was reported by 54.7 %a significant proportion. Taste alteration is a recognized adverse

effect of chemotherapy and can exacerbate nutritional challenges and reduce quality of life[13]. The involvement of inflammatory mediators and salivary changes is implicated in dysgeusia in cancer therapy [13-14].

Periodontitis was observed in 40.7 % of the cohort. The co-occurrence of periodontal inflammation and mucosal injury suggests that baseline periodontal disease may exacerbate or predispose to mucosal injury under chemotherapy. Some authors have posited that pre-existing periodontal status and oral hygiene may influence the severity of mucositis [15], the chronic periodontal inflammation could prime a proinflammatory microenvironment in the oral cavity, thereby synergizing with chemotherapy-induced mucosal damage [16]. In previous studies, the prevalence of mucositis (ulceration, erythema) in chemotherapy patients has ranged from 20 % to 40 % in conventional regimens, rising with intensity, and up to ~55 % in some breast cancer samples (Oral mucositis & oral health related quality of life in women),. the somewhat higher rates in our sample may reflect regional differences, differences in chemotherapy regimens, oral care practices, or patient susceptibilities (nutritional status, comorbidities) [17]. Also, the proportion of patients reporting taste disturbances (54.7 %) is in line with reports that a significant fraction of chemotherapy patients (often > 50 %) manifest dysgeusia [18].

The study indicates that women with oral ulcers, stomatitis, and periodontitis exhibit higher levels of IL-6, MMP-9, and IDO compared to those without these oral manifestations. These findings suggest a potential inflammatory response linked to chemotherapy-induced oral complications. However, specific studies focusing on Iraqi women undergoing chemotherapy are limited to the table 3.

Table. 3 Association Between Oral Manifestations and Biomarker Levels in Chemotherapy-Treated Women (n = 86)

Oral manifestation	Biomarker	Mean ± SD	p-value
Ulcer (n=38) vs. No ulcer (n=48)	IL-6	23.5 ± 5.8 vs. 16.7 ± 4.2	**0.001**
	MMP-9	459.2 ± 68.5 vs. 392.4 ± 70.2	**0.004**
	IDO	2.88 ± 0.71 vs. 2.41 ± 0.63	**0.027**
Stomatitis (n=41) vs. No stomatitis (n=45)	IL-6	21.9 ± 5.9 vs. 17.5 ± 4.6	**0.012**
	MMP-9	447.1 ± 71.4 vs. 459.8 ± 69.5	**0.078**
	IDO	2.79 ± 0.68 vs. 1.39 ± 0.65	**0.084**
Periodontitis (n=35) vs. No periodontitis (n=51)	IL-6	22.4 ± 5.2 vs. 18.2 ± 5.3	**0.016**
	MMP-9	452.3 ± 65.7 vs. 405.6 ± 72.1	**0.022**
	IDO	2.95 ± 0.70 vs. 1.36 ± 0.61	**0.006**

The mean MMP-9 level of ~421.6 ng/mL (SD 72.1) is indicative of elevated extracellular matrix remodeling and proteolytic activity in the oral mucosa under cytotoxic stress. Upregulation of MMP-9 in mucosal tissues following chemotherapy or radiation has been documented in both animal and human studies. [19] showed that MMP-9 expression in oral epithelium increased after irinotecan administration in a rat model of oral mucositis ($p < 0.05$) . Similarly, [20] reported that chemotherapy and inflammatory cytokines may enhance MMP-9 expression in mucosal tissues. Elevated MMP-9 may facilitate breakdown of basement membrane and collagen, promoting ulceration and tissue injury, on the other hand, The mean IL-1β value of 32.7 pg/mL (SD 8.4) falls within a moderate inflammatory range. IL-1β is a key pro-inflammatory cytokine involved in the mucositis cascade: following chemotherapeutic insult, cytokine signaling (including IL-1β) is propagated and amplifies tissue injury, the elevated IL-1β levels have been associated with severity of oral mucositis in clinical settings, serving as a biomarker of mucosal inflammatory burden [9]. The wide range (17 to 50.5) suggests variability in host response among subjects. As well as The average IDO activity of 2.64 ± 0.72 U/mL (range 1.1 to 4.1) points to enhanced tryptophan catabolism via the kynurenine pathway in the study cohort. Indoleamine 2,3-dioxygenase (IDO) is increasingly recognized as an immunoregulatory enzyme that modulates inflammation and immune tolerance [21]. Overexpression of IDO has been implicated in tumor immune escape and suppression of T-cell responses [22]. In inflammatory or cancer settings, elevated IDO may reflect a response to inflammatory signaling and may contribute to local immunosuppressive microenvironments [23]. The range from 1.1 to 4.1 suggests interindividual differences in this metabolic pathway, on the other hand, MDA (mean 4.91 ± 1.38 µmol/L) is a well-established marker of lipid peroxidation and oxidative stress. Its elevation suggests that oxidative damage is present in the mucosal tissues of these patients [24]. In cancer and chemotherapy settings, oxidative stress is a recognized mechanism for mucosal injury and cell membrane disruption [9]. The broad range (2.5 to 7.6) further underscores heterogeneity in oxidative responses across individuals, perhaps influenced by baseline antioxidant status, comorbidities, or chemotherapy dose. Finally, the mean TAC of 0.92 ± 0.21 mmol/L (range 0.5 to 1.4) reflects the antioxidant capacity present in the biological milieu, counteracting free radical damage. Lower TAC values may predispose to more severe mucosal damage under oxidative stress conditions. Some studies in other disease contexts show inverse relationships between TAC and oxidative biomarkers (e.g., in prostate cancer, MDA and TAC have been inversely correlated) [25]. This balance (oxidant vs. antioxidant) is critical in modulating extent of mucosal injury.

DECLARATION

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Conflict of interests

There are no conflicts of interests

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