Original Article

Effects of Systemic Chemotherapy on Tear Volume in Cancer Patients

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Abstract

Purpose: This study aimed to evaluate changes in tear volume and dry eye symptoms in cancer patients following first time systemic chemotherapy.
Patients and Methods: In this cross-sectional study, cancer patients undergoing chemotherapy for the first time with different drug regimens were evaluated before and after treatment. Assessments included the Schirmer's test, the Ocular Surface Disease Index questionnaire, and a comprehensive eye examination for all patients.
Results: A total of 60 patients (120 eyes) with a mean age of 52.07 ± 13.047(range: 18-80 years) were examined. Of these patients 53.3% (n = 32) were female. The mean Schirmer's test score was 9.17 ± 8.65 mm before chemotherapy and 10.02 ± 9.82 mm after chemotherapy; showing no statistically significant difference (P = 0.865). The only group showing a significant increase in mean Schirmer's test score was patients older than 40 years old (P < 0.01).
Conclusion: Although changes in mean tear volume following systemic chemotherapy were not significant - except among patients over 40 years old - further studies with larger sample sizes and longer follow-up periods are warranted.

Keywords: Tear volume; Schirmer's Test; Dry Eeye; Chemotherapy; Cancer.

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Introduction

The incidence of cancer is increasing rapidly [1]. Chemotherapy is one of the most important cancer treatments and may be used alone or in combination with other therapies [2].

Although ocular toxicity from chemotherapy agents is uncommon, some drugs can cause significant ocular complications including dry eye syndrome [3]. The lacrimal layer creates a refractive optical surface and protects the cornea from dryness and infection [4]. The aqueous layer of tears, which constitutes the largest portion of the tear film, is produced by the main and accessory lacrimal glands [5, 6]. Dry eye disease is a multifactorial condition of the tears and ocular surface that can result in discomfort, visual disturbances, and tear film instability, potentially leading to ocular surface damage. It is associated with increased tear film osmolarity and ocular surface inflammation [7]. Dry eye may also develop secondary to an ocular or systemic disease [7, 8]. The prevalence of dry eye disease ranges from 5 % to 35 %, contributing to eye discomfort, reduced visual acuity, and diminished quality of life [9]. Diagnosis is based on clinical manifestations and various diagnostic tests, with the Schirmer's test being one of the most commonly used methods [5].

Ocular symptoms associated with certain chemotherapy drugs include photophobia, decreased vision, foreign body sensation, excessive tearing, dryness, conjunctivitis, abnormal tear production, and epiphora [10, 11]. In some chemotherapy patients, narrowing and occlusion of the lacrimal duct, as well as obstruction of the puncta in the lacrimal drainage system, have been reported [11, 12]. Although most of these complications are transient and treatable, clinicians should be aware of potential ocular toxicity to prevent serious visual impairment through timely intervention. However, only a limited number of studies have investigated this issue.

The present study aimed to evaluate changes in tear volume and dry eye symptoms following the first systemic chemotherapy in cancer patients.

Patients and Methods

This cross-sectional study was conducted on 60 cancer patients whose diagnosis was confirmed by an oncologist. The ethics committee of Shahid Beheshti University of Medical Sciences (Tehran, Iran) approved the study protocol (ethics code: IR. SBMU. RETECH. REC. 1397.1006). Informed consent was obtained from all participants, and the study adhered to the principles of the Declaration of Helsinki.

Patients who were referred for the first time to the chemotherapy ward of Imam Hossein Medical Center in Tehran, Iran, were invited to participate in the study. Volunteer patients, regardless of cancer type and medication regimen, were evaluated for lacrimal system function based on the inclusion criteria before and after systemic chemotherapy.

The inclusion criteria were as follows: having cancer (excluding eye cancer); undergoing elective systemic chemotherapy for the first time; general well-being (Eastern Cooperative Oncology Group [ECOG] Performance Status score: 0-1); [13] absence of eye disease; and age over 18 years. Exclusion criteria included general weakness, concurrent radiotherapy, pre-existing eye diseases, unwillingness to undergo testing, and patient death. The interval between chemotherapy cycles ranged from once a week to once a month (weekly, every two weeks, every three weeks, or monthly), depending on disease type and severity. The study had a follow-up duration of 3 months

or more.

The ocular surface disease index (OSDI) is a valid and reliable tool for diagnosing dry eye disease, with scores ranging from 0 to 100, where higher scores indicate greater disability. Patients are classified as normal, mild, moderate, or severe dry eye based on their score [14]. In this study, a score >13 was considered indicative of dry eye [8, 14], with the following classifications: 0-2, normal; 13-22, mild dry eye; 23-32, moderate dry eye; and 33-100, severe dry eye [14].

The OSDI questionnaire includes 12 questions categorized into three sections: eye symptoms (3 questions), vision-dependent functions (6 questions), and environmental stimuli (3 questions), as detailed in table 1. The final ODSI score is calculated using this equation OSDI score = sum of scores for questions answered multiplied by 25 and then divided by the number of questions answered.

Tear volume was measured using the Schirmer's 1 test (without local anesthesia). A Schirmer's test strip (35 × 5 mm) was placed on the outer third of the lower eyelid fornix under dim light with the patient's eyes closed. After five minutes, the amount of paper wetting was measured in millimeters [5, 14]. The Schirmer's 1 test was chosen to avoid any pharmacological influence on the results. Measurements were performed simultaneously for both eyes. Since different results were obtained for each eye, both were analyzed.

Comprehensive ocular and visual assessments were conducted for each patient. To avoid influencing test results, the Schirmer's test was performed before other evaluations. It is recommended that this test be conducted with the eyes closed, as tear production is higher with open eyes [15]. Schirmer's test 1 results

Table 1: The OSDI questionnaire and its proposed scoring system

Category	Questions	Minimum	Maximum
Ocular symptoms	1. Eyes sensitive to light?	0.00	4.00
	2. Eyes feeling gritty?	0.00	4.00
	3. Painful or sore eyes?	0.00	4.00
Vision-related function	4. Blurred vision?	0.00	4.00
	5. Poor vision?	0.00	4.00
	6. Reading?	0.00	4.00
	7. Driving at night?	0.00	4.00
	8. Working with a computer or bank machine (ATM)?	0.00	4.00
	9. Watching TV?	0.00	4.00
Environmental triggers	10. Windy conditions?	0.00	4.00
	11. Places or areas with low humidity (very dry)?	0.00	4.00
	12. Areas that are air conditioned?	0.00	4.00

were interpreted as follows: severe dry eye, ≤ 2 mm; moderate dry eye, ≤ 5 mm; mild dry eye, ≤ 10 mm; and normal, >10 mm [4].

To minimize bias, patient participation was voluntary and facilitated by nurses. Additionally, treatment plans, including medications and follow-ups, were unknown to the researcher and were managed by the oncologist. All visual and ocular examinations were conducted by the same examiner, using the same devices and in the same location, between 8 AM and 2 PM.

Statistical analysis

Data were statistically analyzed using SPSS version 23.0 (IBM, Armonk, New York). The normality of Schirmer's test results (before and after chemotherapy) and questionnaire scores was assessed using the Shapiro-Wilk test, which indicated a lack of normal distribution. Therefore, the non-parametric Wilcoxon test and Mann-Whitney U test were used for data analysis. Statistical significance was set at $\alpha = 0.05$.

Results

A total of 120 eyes from 60 cancer patients with a mean age of 52.07 ± 13.05 (range: 18 - 80 years) were evaluated in this study, 80 % of whom were over 40 years of age. Overall, 53.3 % (n = 32) of the patients were female, and 46.7 % (n = 28) were male. The mean age of male participants was (53.82 ± 15.11), while the mean age of female participants was 50.53 ± 10.82 years. The 40-60 age group had the highest frequency (56.7 %).

Patients used different types of chemotherapy medications, with the most common regimen being Carboplatin and Taxol (30 %). Additionally, different types of cancer were included, the most common being gastrointestinal cancer (23.3 %).

In this study, the Schirmer's test scores ranged from 0 to 35 mm. Based on the non-parametric Wilcoxon test, no significant difference was observed in Schirmer's test scores before and after chemotherapy (P = 0.865). A comparison of mean Schirmer's and OSDI test scores before and after chemotherapy in different age groups is presented in table 2. The only difference was observed in age group > 40 indicating significantly higher Schirmer's test results after treatment in this age group (P < 0.01).

A comparison of mean Schirmer's and OSDI test scores before and after chemotherapy based on sex is presented in table 3. No

Table 2: Comparison of the mean of Schirmer's and OSDI test scores before and after chemotherapy based on the age group

Age group	Schirmer before (mm)	Schirmer after (mm)	P value	OSDI before	OSDI after	*P value
< 40	10.67 ± 8.78	11.46 ± 12.43	0.609	0.262 ± 0.93	0.184 ± 1.23	0.65
> 40	8.79 ± 8.62	9.67 ± 9.10	0 < 0.01	0.363 ± 1.81	1.63 ± 6.64	0.180
Total	9.17 ± 8.65	10.02 ± 9.82	0.865	0.28 ± 1.60	1.28 ± 5.88	0.157
*P value	0.134	0.606		0.541	0.597	0.447

* Based on Wilcoxon test

Table 3: Comparison of the mean of Schirmer's and OSDI test scores before and after chemotherapy based on sex

Gender	Statistic	Schirmer before (mm)	Schirmer after (mm)	P value	OSDI before	OSDI after	P value
Female	Mean ± SD	9.09 ± 8.58	10.86 ± 10.61	0.592	0.32 ± 1.14	1.22 ± 1.66	0.317
Male	Mean ± SD	9.25 ± 8.78	9.07 ± 8.84	0.390	0.43 ± 1.23	1.60 ± 2.23	0.384
P value *		0.985	0.512		0.378	0.892	

* Based on Wilcoxon test

Table 4: Comparison of the frequency of dry eye before and after systemic chemotherapy

Variable		Before	After	P value *
Dry eye severity	Mild	28 (23.3)	28 (23.3)	0.41
	Moderate	30 (25.0)	28 (23.3)	
	Severe	42 (35.0)	40 (33.3)	
	Normal	20 (16.7)	24 (20.0)	

* Based on Mann-Whitney U test

significant difference was observed between the before and after results.

A comparison of dry eye severity frequencies (expressed as percentages) is presented in table 4. Again no significant difference was observed between the before and after results.

Discussion

In this study, the effects of systemic chemotherapy on tear volume were evaluated prospectively, before and after the first course of chemotherapy. The OSDI questionnaire was used to assess patients' subjective symptoms after chemotherapy, while Schirmer's test was used to estimate tear volume [15].

The ocular side effects of chemotherapy range from minor and transient symptoms to complete and irreversible blindness [16]. Dry eye disease has been reported as an adverse response to chemotherapy [17]. Anastrozole, Nilotinib, Methotrexate, and 5-Fluorouracil can induce dry eye disease [18, 19]. Peripheral nerve damage caused by Paclitaxel can also exacerbate dry eye disease symptoms [20]. Immunological alterations, including changes in cell cytotoxicity due to antibodies or the accumulation of degradation products, might primarily contribute to dry eye disease and meibomian gland dysfunction. Additionally, hormonal dysregulation can lead to dry eye disease [18]. However, few studies have evaluated tear volume changes following chemotherapy in cancer patients.

In the present study, according to Schirmer's test scores, the prevalence of mild and moderate dry eye was lower than that of severe dry eye both before and after chemotherapy. Some previous studies on dry eye syndrome indicate that most affected patients have mild symptoms [21]. The higher prevalence of severe dry eye in this study suggests that patients with cancer or those undergoing chemotherapy may experience more severe symptoms.

Comparison of Tear Volume before and after Chemotherapy

A comparison of mean Schirmer's test scores

before and after chemotherapy showed that tear volume did not significantly change after chemotherapy except for among patients over 40 years old. Although the present results suggest no change in tear volume in the participants as a whole, further studies on a larger cancer patient population are needed. Since a Schirmer's test score < 10 mm (without anesthesia) is considered abnormal [18], most participants had dry eye.

Variations in increased or decreased tear volume were observed, with low frequency, which may be attributed to individual patient characteristics and reactions to treatment.

Chemotherapy-induced changes in the lacrimal system have been reported, leading to both symptomatic and clinical ocular manifestations [19]. Tearing has been observed in patients receiving 5-Fluorouracil and Doxorubicin, which gradually resolves after discontinuation of these medications [20]. Additionally, epiphora and increased tearing have been reported in patients receiving weekly Docetaxel injections, even at approved dosage levels [21, 22].

Chemotherapeutic agents may negatively affect the lacrimal drainage system due to drug secretion in tears, leading to local inflammation or other less well-known mechanisms [23]. Meibomian gland dysfunction causes evaporative dry eye disease and can induce reflex tearing [24]. Reflex tearing is an important cause of excessive tearing in patients undergoing chemotherapy [25]. The chemotherapeutic agent 5-Fluorouracil (5FU) may cause lacrimal gland fibrosis, canalicular edema, and meibomian gland dysfunction [26- 28]. Pertuzumab has been associated with increased lacrimation and may also cause signs and symptoms of anterior segment toxicity, including dry eyes [29-30].

Subjective Versus Objective Symptoms of Dry Eye

The mean OSDI score was low among our patients, indicating that patients reported few complaints. A comparison of Schirmer's test and OSDI scores showed that subjective symptoms were far fewer than objective findings, which may be due to several factors. Many cancer patients experience more severe systemic symptoms, making ocular discomfort seem less significant.

According to questionnaire results, visual disturbances were the most common complaint. This may be due to the high proportion of elderly participants, as tear film instability can cause refractive irregularities, leading to blurred vision [8]. Additionally, patients responded to fewer environmental stimuli questions, possibly because they were less exposed to external irritants (e.g., wind) due to their medical condition.

Previous Studies on Chemotherapy and Dry Eye

A previous study assessing first-time chemotherapy patients found that dry eyes, eye pain, infection, itching, redness, tearing, and eye heaviness were common complaints [31]. Another study reported that 4 out of 13 patients receiving high-dose Methotrexate experienced recurrent ocular irritation (burning, itching, dry eye) within two to seven days after chemotherapy [32].

In a study evaluating the prevalence of symptomatic dry eye in women undergoing adjuvant chemotherapy for breast cancer, OSDI was used. Results showed that 59 % of patients had symptomatic dry eye, and 71 % of those who received more than four courses of chemotherapy experienced moderate to severe dry eye. A significant relationship was found

between treatment duration and symptom severity [33].

Study Limitations

Present study limitations include variability in treatment regimens and dosing intervals. Larger multi-cancer and multi-drug studies are needed to better understand the effect of different cancers and drug regiments on dry eye.

Conclusion

Although changes in mean tear volume following systemic chemotherapy were not significant - except among patients over 40 years old - further studies with larger sample sizes and longer follow-up periods are warranted.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.