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ORIGINAL ARTICLE

Hyposmia: an underestimated and frequent adverse effect of chemotherapy

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Abstract
Objectives Optimal function of both the olfactory sensory neurons and the olfactory mucosa is a prerequisite for normal olfactory perception. Both the olfactory neurons and mucosa might be subjects to the neurotoxic and mucotoxic effects of chemotherapy. Despite the recognized importance of olfaction in nutrition and quality of life, the potential olfactory toxicity of chemotherapy regimens has not been adequately assessed. The aim of this study is to investigate whether mucotoxic and/or neurotoxic drugs compromise olfactory performance.
Patients and methods Forty-four consecutive patients completed the "Sniffin' Sticks" test, an objective quantitative/qualitative method to assess olfactory function, at diagnosis and immediately before the infusion of the last session of three to four chemotherapy cycles, according to the therapeutic protocol. The patients underwent therapy containing oxaliplatin and antimetabolites (5-FU or capecitabine; O+A group), taxanes and platinum analogues (cisplatin and carboplatin; T+P group), or taxanes and anthracyclines (doxorubicin or liposomal doxorubicin; T+A group).
Results A significant decrease was noted for olfactory threshold (OT), olfactory discrimination (OD), olfactory identification (OI), and the composite threshold–discrimination–identification (TDI) score. A significant deterioration of all olfactory indices was found for each chemotherapy group. Pairwise comparisons revealed significant differences between the O+A and the T+P group regarding OT and TDI. TDI scores were significantly lower after chemotherapy in all age groups. Patients older than 50 years were found to be more susceptible to olfactory toxicity than younger patients.
Conclusions Patients who undergo chemotherapy experience significant compromise in their olfactory function. A grading system for olfactory toxicity is proposed.

Keywords Sniffin' Sticks test · Hyposmia · Olfaction · Chemotherapy · Toxicity

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Introduction

Smell dysfunction may play an important role in patients' health and quality of life by affecting food intake and appetite. Olfactory disorders in the oncology setting have not been sufficiently studied, thus remaining underdiagnosed and underestimated in clinical practice. The relevant literature is quite limited and conflicting. In most of the existing studies, alterations in smell acuity are assessed through structured interviews and self-reported questionnaires [1]. However, humans have proven to be quite poor at assessing their olfactory acuity [2]. As far as olfactory function is concerned, self-ratings seem to correlate with *odor annoyance* rather than true olfactory efficiency or hyperosmia [3–5]. There is a substantial difference between the two, with odor annoyance being more cognitive (central level) than sensory (peripheral level) and odor sensitivity being more sensory than cognitive. This determinant seems to dictate the need for more quantitative studies in order to assess the adverse effects of chemotherapy on olfaction [6].

Few studies have evaluated the olfactory function based on a quantitative and qualitative procedure (such as Sniffin' Sticks), however, with controversial results and in highly selected populations undergoing either platinum-based or anthracycline-based regimens [7–9]. The aim of this study is to demonstrate the short-term effects of chemotherapy on olfactory sensitivity. Taxanes, platinum compounds, antimetabolites, and anthracyclines are evaluated and compared with regard to their effect on olfactory thresholds, odor discrimination, and odor identification efficiency. The results are discussed in view of their clinical implications and their possible role in supportive care.

Patients and methods

Inclusion criteria The main inclusion criteria were as follows: (a) no history of rhinological disease (including allergic rhinitis), surgery of the nose/paranasal sinuses, or major head trauma; (b) no cranial irradiation; and (c) no brain tumor or metastases. Patients with diabetes were also excluded, because of their known predisposition for developing a chemotherapy-induced neuropathy [10]. All patients fulfilling the inclusion criteria were approached, and no patient refused to take part in a baseline evaluation. The treating oncologists first recruited the patients, providing them a short description of the examination process. All tests were then performed by one otorhinolaryngologist, after having explained any further details of the examination procedure and obtained the patients' informed consent during the baseline evaluation session. Fifty consecutive patients were initially recruited. Two patients refused to complete the follow-up examination because they developed increased odor annoyance. Four patients were excluded because they developed central nervous system comorbidities or because there was a modification of their therapeutical regime, leaving 44 patients for final evaluation.

Patient characteristics The demographical and oncological characteristics of the patients are presented in Table 1. The patients were divided into three groups according to the administered chemotherapy regimen. One group consisted of patients undergoing therapy containing oxaliplatin and antimetabolites (5-FU/capecitabine or gemcitabine; O+A group). The second group included patients who received taxanes and platinum-containing regimens (carboplatin or cisplatin; T+P group) and the third group taxanes and anthracyclines (doxorubicin or liposomal doxorubicin; T+A group). The patients were also assigned into three age groups 39–50, 51–62, and 63–73 years.

Evaluation of olfactory function All subjects completed the "Sniffin' Sticks" test (Burghardt, Wedel, Germany) at diagnosis and immediately before the infusion of the last session of three to four chemotherapy cycles, according to the therapeutic protocol (the median time between baseline and follow-up examination±SD=4±1.4 months). All tests were performed in the same quiet, well-ventilated room, under similar conditions of temperature and humidity. The patients were instructed not to have eaten or drunk anything other than water 15 min prior to the measurements. This rule extended also to smoking and the use of drops or chewing gum.

Table 1 The demographical and oncological characteristics of the patients included in the study

Characteristic		Patients (n=44)
Gender	Male	17 (39 %)
	Female	27 (61 %)
Age group (years)	39–50	6 (14 %)
	51–62	15 (34 %)
	63–73	23 (52 %)
Histological diagnosis	Breast	20 (45 %)
	Gastrointestinal	11 (25 %)
	Lung	9 (20 %)
	Ovarian	4 (10 %)
Chemotherapeutical regimen	T+A	11 (25 %)
	O+A	15 (34 %)
	T+P	18 (41 %)
Smoking	Yes	17 (39 %)
	No	27 (61 %)

T+A taxanes and anthracyclines, *O+A* oxaliplatin and antimetabolites, *T+P* taxanes and platinum analogues

The Sniffin' Sticks test comprises three tests of olfactory function, namely, tests for odor threshold (*n*-butanol, testing by means of a single staircase), odor discrimination (16 pairs of odorants, triple-forced choice), and odor identification (16 common odorants, multiple-forced choice from four verbal items per test odorant). Previous work has already established its test–retest reliability and its validity in comparison with established measures of olfactory sensitivity obtained by the University of Pennsylvania Smell Identification Test (UPSIT), the Connecticut Chemosensory Clinical Research Center (CCCRC), and the Cross-Cultural Smell Identification Test (CC-SIT) [11, 12]. The test battery consisted of three examinations, odor threshold (OT), suprathreshold odor discrimination (OD), and odor identification (OI). OT was assessed using *n*-butanol as the odorant, with the dilutions being established in a geometric series. Using a triple-forced-choice paradigm, detection thresholds were determined by employing a single staircase method. OD was performed by means of 16 triplets of odorants. The subject was presented with three odorants and was asked to identify the sample that had a different smell. OI was assessed by means of 16 common odors, with the patient being asked to identify the odor among four possible answers presented by the examiner. The overall score is called

"composite threshold–discrimination–identification" (TDI) score and is usually used to characterize olfactory acuity as normosmia, hyposmia, or hyperosmia [11]. The TDI score ranges from 0 to 48 with values ≤15 considered consistent with functional anosmia. In the mild climate conditions of Greece, the TDI score at the 10th percentile which defines the limit between normosmia and hyposmia was found to be 39.5 for ages from 36 to 55 years and 30.75 for subjects older than 55 years [13]. The 10th percentile values for OT, OD, and OI for the age group 36–55 years are 8.5, 15, and 14, respectively, and for the older than 55 years age group 5.75, 13, and 12, respectively. Self-rating of olfaction as normal, decreased, or increased was also noted at the beginning of each examination.

Statistical analysis Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS), version 21.0. The normality assumption was tested with the Shapiro–Wilk test. The related-samples Wilcoxon signed-rank test was used to evaluate the median differences between pre- and post-chemotherapy TDI, OT, OD, and OI scores. The related-samples Hodges–Lehman test was used to calculate 95 % confidence interval (95 % CI). The independent-samples Kruskal–Wallis test was used to test the null hypothesis that the distribution of TDI, OT, OD, and OI is the same across chemotherapy groups and makes pairwise comparisons. The Mann–Whitney *U* test was used to evaluate the effect of smoking and gender. All tests were two tailed, and statistical significance was considered for p values <0.05.

The study was approved by the Institutional Review Board of the University Hospital of Evros and is in compliance with the Declaration of Helsinki.

Results

Subjective perception of olfactory acuity The study population (Table 1) included 44 patients with a median age of 60 years (mean age±standard deviation=60±8.4 years; range 39–73 years). At baseline examination, all patients self-rated their olfactory acuity as normal. Ten (22.7 %) patients were, however, found to be hyposmic at baseline examination due to heavy smoking and/or old age. At follow-up examination, hyposmia was diagnosed in 42/44 patients. Nevertheless, only 7/42 (16.7 %) patients perceived their olfactory function as decreased, with 6 of them being diagnosed as anosmic (TDI <15) in the Sniffin' Sticks test which followed. Three more patients (7.1 %) reported an increase in their olfactory acuity, while their TDI scores indicated hyposmia.

Composite threshold–discrimination–identification scores Since the normality assumption was violated, nonparametric tests were used for statistical analysis. A statistically significant decrement of TDI score was noted in the population of the study (Wilcoxon signed-rank, p=0.0001, 95 % CI=−14.63 to −11.38) (Fig. 1). The difference between post- and pre-chemotherapy TDI scores was negative in all but one patient. At the end of chemotherapy, all but two patients had turned hyposmic or anosmic, while at the beginning, hyposmia was documented in 10 patients. TDI scores exhibited a highly significant decrease in all three chemotherapy groups (Table 2). Pairwise comparisons are presented in Table 3. In terms of TDI scores, older patients performed worse in pre-chemotherapy measurements (p=0.04, Kruskal–Wallis). All age groups demonstrated a significant decrease in their TDI scores (p=0.043, 0.0001, and 0.0001, respectively, with ascending age order). Smoking and gender were not found to affect the changes in any of the olfactory indices (TDI, OT, OD, OI).

Olfactory threshold OT scores showed a similar descending trend (Wilcoxon signed-rank, p=0.0001, 95 % CI=−3.13 to −1.63) (Fig. 1). Negative differences were noted in 36/44 patients. The age group 39–50 years demonstrated no significant decrease in TDI scores, while older patients presented a significant decrease in their OT scores (Wilcoxon signed-rank, p=0.005 and 0.001, respectively, with ascending age order). Results across chemotherapy groups are presented in Tables 2 and 3.

Olfactory discrimination OD scores were also significantly decreased due to chemotherapy (Wilcoxon signed-rank, p=0.0001, 95 % CI=−6 to −5) (Fig. 1), with negative post- and pre-chemotherapy differences being noted in 42/44 patients. All age groups demonstrated a significant decrease in their OD scores (p=0.041, 0.0001, and 0.0001, respectively, with ascending age order).

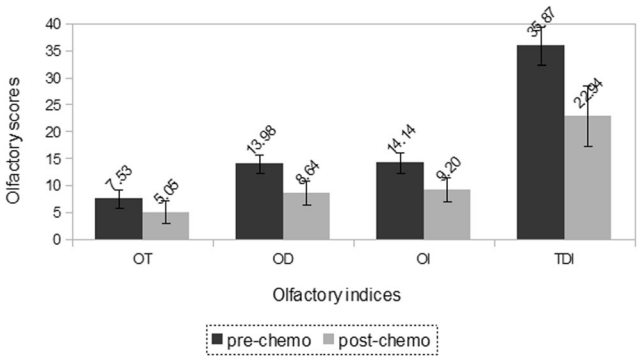

Fig. 1 Olfactory performance before and after chemotherapy. *OT* olfactory threshold, *OD* olfactory discrimination, *OI* olfactory identification, *TDI* composite threshold–discrimination–identification score. *Error bars* represent standard deviation. Differences were significant for all olfactory indices (Wilcoxon signed-rank, p=0.0001)

Table 2 Olfactory performance across different chemotherapy groups

Olfactory indices across groups		T+A		O+A		T+P	
		Scores	*p*	Scores	*p*	Scores	*p*
OT	Pre-chemo	8.35±2.65	0.014	7.47±1.88	0.002	7.18±0.89	0.015
	Post-chemo	5.28±1.83		4.15±2.05		5.75±2.02	
OD	Pre-chemo	14.7±1.16	0.005	13.47±2.03	0.001	14.06±1.59	0.0001
	Post-chemo	9.6±2.37		7.73±1.71		9.06±2.21	
OI	Pre-chemo	14.8±2.15	0.007	13.73±1.67	0.001	14.39±1.42	0.0001
	Post-chemo	10.10±1.91		8.27±2.34		9.61±1.94	
TDI	Pre-chemo	37.85±1.59	0.005	34.67±4.17	0.001	36.18±3.14	0.0001
	Post-chemo	24.98±4.93		20.15±5.68		24.53±5	

p values attributed through related-samples Wilcoxon signed-rank test. Scores represent mean values±standard deviation

OT olfactory threshold, *OD* olfactory discrimination, *OI* olfactory identification, *TDI* composite threshold–discrimination–identification score, *T+A* taxanes and anthracyclines, *O+A* oxaliplatin and antimetabolites, *T+P* taxanes and platinum analogues

Olfactory identification A significant reduction of OI scores was demonstrated for the overall study population (Wilcoxon signed-rank, $p=0.0001$, 95 % CI=−5.5 to −4.5) (Fig. 1). Negative post- and pre-chemotherapy differences were noted in 43/44 patients. All age groups demonstrated a significant decrease in their OI scores ($p=0.042$, 0.0001, and 0.0001, respectively, with ascending age order).

Discussion

Olfactory dysfunction in cancer patients has not been thoroughly studied, and practically no effort is made to alleviate olfactory alterations caused by cytotoxic drugs. This is partly due to the fact that the evaluation of olfactory function is mostly based on self-rating [1]. Nevertheless, as shown in the present study, patients undergoing chemotherapy are usually not aware of the significant compromise in all indices of their olfactory function (identification, discrimination, and threshold) (Fig. 1), until they have reached the levels of anosmia. In this respect, cancer patients are no exception to a general rule that humans pay little attention to their olfactory incoming stimuli [5]. Nevertheless, humans actually possess a superb sense of smell that subconsciously affects quality of life, mood, physiological state, cognitive performance, and sexual and social behavior [5, 14–16] and contributes to avoidance of health risks, such as spoiled food or leaking natural gas. Furthermore, olfactory sensitivity restrictions are known to have a direct association with taste disturbance and loss of pleasure from eating [17–19]. Thus, olfactory dysfunction may contribute to the malnutrition problems of patients undergoing chemotherapy, along with other factors such as gustatory dysfunction, intractable emesis, hormonal alterations, and the syndrome of cancer cachexia.

To date, three previous studies have attempted to assess quantitatively olfactory disorders in patients undergoing chemotherapy [7–9]. Yakirevitch et al. [9] studied the olfactory changes in 21 patients treated with cisplatin-based regimens (in combination with 5-fluorouracil, etoposide, or temozolomide) without finding any decrease in olfactory performance neither during chemotherapy nor 3 weeks after the end of treatment. On the other hand, Steinbach et al. [8], who enrolled 12 ovarian cancer patients treated with carboplatinum plus paclitaxel, noted a significant decrease in TDI scores during chemotherapy, which might mainly be attributed to the neurotoxic effects of paclitaxel. Although no detailed analysis of the OD and OI scores is provided, chemotherapy seemed to have a substantial effect on OT scores. In the present study, the combination of taxanes and platinum derivatives was also found to significantly affect TDI scores. Moreover, an analysis of all four olfactory indices revealed a significant decrease at the end of chemotherapy in all cases (TDI, OT, OD, and OI) (Table 2). Little is known about the mechanisms responsible for the development of neuropathy. A general

Table 3 Pairwise comparisons of olfactory performance among different chemotherapy groups after the administration of chemotherapy

	OT	OD	OI	TDI
Same distribution across groups pre-chemo	NS	NS	NS	NS
Same distribution across groups post-chemo	0.016	NS	0.033	0.014
O+A vs T+A	NS	NS	NS	NS
O+A vs T+P	0.014	NS	NS	0.022
T+P vs T+A	NS	NS	NS	NS

p values attributed through independent-samples Kruskal–Wallis test (significance adjusted for baseline scores). Statistical analysis was performed on the results presented in Table 2 and Fig. 1

NS non significant, *OT* olfactory threshold, *OD* olfactory discrimination, *OI* olfactory identification, *TDI* composite threshold–discrimination–identification score *T+A* taxanes and anthracyclines, *O+A* oxaliplatin and antimetabolites, *T+P* taxanes and platinum

predisposition for developing a chemotherapy-induced neuropathy has been observed in nerves previously damaged by diabetes mellitus, alcohol, or inherited neuropathy [12, 20]. Patients with those predisposing factors were excluded from the study.

In the remaining two groups of the present study, neurotoxic agents, such as oxaliplatin and taxanes, are combined with chemotherapeutics that are known to induce mucosa barrier injury (mucositis), such as antimetabolites and anthracyclines, respectively (groups O+A and T+A) [20, 21]. Nasal patency and optimal function of both the olfactory sensory neurons and the olfactory mucosa are all important for normal olfactory perception. The nasal mucosa plays a key role in olfaction both through the production of odorant-binding proteins that act to facilitate odorant–receptor interaction and clearance, as well as through providing an appropriate local environment for optimal signal transduction [22]. Patients of both O+A and T+A groups were diagnosed with significant compromise in all four olfactory indices at the end of chemotherapy (Table 2). A cohort undergoing T+A chemotherapy was also studied by Steinbach et al. [7] as part of a general population diagnosed with breast cancer or gynecologic malignancies and undergoing therapy with anthracycline-containing, T+A-containing, or platinum-containing regimens. Although the authors do not provide a group-by-group analysis, they conclude that for all chemotherapeutic substances, there was a significant decrease of olfactory function during chemotherapy.

An estimation of a possible interaction between chemotherapeutic agents was attempted (Table 3). While the distribution of all olfactory scores was similar among groups before chemotherapy, significant differences were noted after chemotherapy for OT, OI, and TDI. Pairwise comparisons attributed significant differences between O+A and T+P groups with respect to OT and TDI. Although referring to limited numbers of patients, a possible cumulative olfactory toxicity that might result from combining neurotoxic with mucotoxic drugs might merit further investigation in larger populations. Comparisons of the T+A group with both O+A and T+P groups revealed no significant differences. Comparisons between T+A-containing, anthracycline-containing, and platinum-containing regimens also showed no significant differences when performed in the study population of Steinbach et al. [7].

In the population of this study, older patients exhibited marked deterioration of all olfactory indices, while patients aged less than 50 years presented marginal attenuation of their OD, OI, and TDI scores ($p=0.04$) and nonsignificant decrease in their OT scores. Older age has been associated with decreased numbers of olfactory receptor cells and reduced regeneration capacities, as well as reduced mucus secretion and changes in epithelial thickness [23]. Steinbach et al. [7] also indicated that older patients seem to be more susceptible to olfactory disorders. These patients might benefit from a relevant alleviating care, such as steroids administered systemically or topically, a common therapeutical choice among patients with hyposmia/anosmia of various etiologies [24].

Table 4 Proposed grading for olfactory toxicity

Grade	Olfactory toxicity
0	Normosmia
1	Asymptomatic hyposmia; established through quantitative objective measurements; intervention not indicated
2	Symptomatic hyposmia; limiting age-appropriate activities of daily living (such as preparing meals, food tasting, detecting spoiled food); treatment indicated
3	Anosmia; established through quantitative objective measurements; treatment indicated
4	Not applicable
5	Not applicable

Accumulating evidence seems to indicate that olfactory sensitivity is subject to significant decline during chemotherapy with most of the currently administered chemotherapeutical regimens (neurotoxic and/or mucotoxic). With olfactory dysfunction being recognized as an adverse effect of chemotherapy, a need for a quantitative and objective grading system emerges, which may serve for clinical evaluation, as well as research, comparisons among different regimes, and patient follow-up and counseling. Such a grading system is currently lacking. In accordance with the general principles of the Common Terminology Criteria for Adverse Events (Version 4.0, 2009), olfactory toxicity may be graded with respect to quantitative evaluation and clinical observations. Such a proposal is presented in Table 4.

Conclusions

Olfactory disorders remain an unexplored field in supportive care in cancer. There is accumulating evidence that patients who undergo chemotherapy experience a significant compromise in their olfactory sensitivity and their ability to identify and discriminate odors. Given the well-known association of olfaction with appetite, food intake, nutrition, and quality of life, olfactory disorders in cancer patients and the possible ways to alleviate them may merit further investigation. The incorporation of olfactory disorders between the common side effects of chemotherapy and their monitoring through an appropriate grading system are important

steps toward the investigation of their pathophysiology and clinical implications.

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