Eur Arch Otorhinolaryngol (2017) 274:2813–2818
DOI 10.1007/s00405-017-4559-y

RHINOLOGY

Testicular cancer patients undergoing cisplatin based chemotherapy exhibit temporary olfactory threshold scores changes

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Received: 13 February 2017 / Accepted: 30 March 2017 / Published online: 20 April 2017

Abstract Testicular cancer is the most frequent malignant disease in young males between 15 and 35 years. Platinum based chemotherapy regimen is the therapy of choice in advanced disease. This treatment has also adverse effects caused by the cytostatic active substances, such as olfactory dysfunctions. The aim of this study was, therefore, to monitor olfactory function of testicular cancer patients during and 6 months after chemotherapy. A total of 17 patients (mean age 31.06 ± 10.26 years), which underwent chemotherapy (mean 2.47 cycles ± 0.5) were enrolled in this study. Odor threshold, discrimination and identification were assessed by means of the "Sniffin' Sticks" prior to and on day 42, 90 and 180 after chemotherapy has been completed. Furthermore, patients' ratings of olfactory function and depressive symptoms were evaluated. Threshold scores were significantly lower on day 90 (8.0 ± 2.51) compared to baseline (10.4 ± 2.20) ($p = 0.014$) and recovered almost completely on day 180 (9.65 ± 3.26). Odor discrimination and identification did not show significant changes during therapy. The decrease of the olfactory function during/immediately after chemotherapy was underlined by the subjectively perceived impaired olfactory function during this time. In addition almost every fourth patient presented with a depressed mood at the beginning of chemotherapy. Patients should be informed about possible transient olfactory impairment during/immediately after chemotherapy.

Keywords Smell · Olfaction · Sniffin' Sticks · Platinum based chemotherapy

Introduction

Testicular tumors are the most frequent malignant diseases in men aged between 15 and 35 [1]. Cisplatin-based combination chemotherapy and—if indicated—surgical removal of residual disease is the standard treatment for metastatic germ cell tumors. This treatment cures a vast majority of patients. Besides the achievements obtained through chemotherapy, there also exist adverse effects caused by the cytostatic active substances, such as possible changes of olfaction in patients. There are several studies indicating the presence of subjective decrease in the sense of smell in cancer patients treated with chemotherapy [2–4]. As the subjective rating of olfactory function has been shown to be notoriously inaccurate, it is necessary to measure olfactory function [5]. There are some studies which measured olfactory function psychophysically during versus after chemotherapy with inconclusive findings though [2–14]. However, chemosensory alterations, especially olfactory and taste distortions have been reported in cancer patients in general. These findings are important as they may lead to a reduced pleasure of eating, resulting in lower energy intake, weight loss, nausea enhancing malnutrition and eventually morbidity in cancer patients

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[15–18]. This can furthermore result in higher levels of distress and in consequence to a strong decrease in quality of life [2, 17], which is more severely perceived in younger patients with impaired sense of smell compared to older patients [19–21]. This is especially interesting for testicular cancer patients as this disease affects mostly younger males. Knowing about possible olfactory dysfunction in testicular tumor patients undergoing chemotherapy, physicians could strengthen screening for this pathology and could intensify help for the affected patients. Patients could benefit from flavor enhancement, chemosensory education, and nutritional information, as this has already been shown to be beneficial for older cancer patients [22]. In summary, there are several reasons why investigation of the sense of smell of cancer patients receiving chemotherapy is important. The aim of the present study was, therefore, to analyze olfactory function of testicular patients before, during and after cisplatinum based chemotherapy. In addition depression markers were recorded and analyzed, as well.

Materials and methods

The present study was performed at the Smell & Taste Clinic of the Department of Otorhinolaryngology at the "Technische Universität Dresden" (TU Dresden) and approved by the local ethics committee (EK204072009). Written informed consent was obtained from all participants.

Participants

A total of 28 patients, suffering from testicular tumors were prospectively evaluated for the present study. Only participants who finished the last follow-up (21 of 28 patients) and whose baseline olfaction was normosmic (TDI score >30.75) (17 of 21 patients) were considered appropriate for this study and statistically analyzed. All patients underwent either the BEP (cisplatin, etoposid, bleomycin) or VIP (etoposide + ifosfamide + cisplatin − under mesna protection) chemotherapy protocol. Patients with acute or chronic rhinosinustis, neurological and olfactory disorders were excluded. In addition none of them had comorbidities that might affect olfaction such as hyper- or hypothyreoidism, liver or renal problems, or diabetes.

Study protocol

Olfactory function was assessed one day before (day 0), during (day 42), shortly after (day 90) and 6 months (day 180) after chemotherapy. Additionally, patients were asked to respond to a questionnaire to assess their subjective chemosensory symptoms (olfaction, phantosmia, parosmia) and depressive symptoms for the same dates.

Olfactory testing

Orthonasal olfactory function was measured by means of the validated extended Sniffin' Sticks test battery (Burghart GmbH, Wedel, Germany) [23] which consists of three separate subtests: phenylethylalcohol (PEA) odor threshold (THR), odor discrimination (DIS), and odor identification (ID). Results of the three subtests are summed up for a composite TDI score. This validated test is based on pen-like odor-dispensing devices [24]. For odor testing the cap of the pen was removed for approximately 3 s and the felt-tip was presented approximately 2 cm in front of the subjects' nostrils. Testing started with the threshold subtest, where 16 dilutions were used. The participants were presented a stick triplet, with one containing the odor (PEA-rose like smell) and the others containing solvent, propylene glycol, alone. Triplets were presented in increasing odor concentrations, starting with the lowest one. After identifying the correct (odor containing) pen twice in a presented triplet, a reversal of the staircase was started until the patient could no longer identify the odor containing pen. The threshold score was built from the mean of the last four out of seven staircase reversals.

For the DIS, 16 triplets were presented, with two pens containing the same odor and the third a different one, which was asked to be identified by the patient. The last subtest performed was the ID, where 16 pens with different odors were presented. Individuals were asked to choose the object that describes the odor the best through multiple forced choice from flash cards where the name of the objects were written.

Subjective assessment

On a 5 point Likert scale, patients rated their subjective olfactory function (complete loss, impaired sense of smell, normal, better than normal, excellent). Furthermore, they were asked whether they notice odors in absence of an odor source (phantosmia) or whether known odor sources exhibit an altered scent (parosmia).

Beck depression inventory

Patients were in addition asked to fill out the Beck Depression Inventory (BDI) test, which is a widely used, standardized and validated tool used for measuring depressive symptoms [25, 26]. The BDI consists of 21 questions in a 4-item forced choice manner. Answer possibilities were scored from 0 (= no stress present) to 3 points (= maximal stress present) resulting in a sum score

between 0 and 63 points. A BDI score <11 reflects the norm, whereas a score between 11 and 17 points suggests a moderate manifestation of depressive symptoms and a score ≥18 indicates a relevant manifestation of depressive symptoms.

Statistical analysis

Statistical analysis was performed by means of SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Repeated measures ANOVAs were performed. Greenhouse-Geisser corrected degrees of freedom were used when the sphericity assumption was infringed. Bonferroni tests were used for post hoc comparisons. p values of <0.05 were considered significant.

Results

The study population comprised a total of 17 patients, suffering from testicular cancer (3 seminoma patients, 1 recurrent seminoma and 13 nonseminoma patients), with a mean age of 31 years ± 10 years (range 18–60 years), which were prospectively included in the present study. Patients underwent in mean 2.47 cycles ± 0.5 (range 2–3 cycles) of chemotherapy.

Olfactory assessment

At baseline examination patients obtained a mean THR score of 10.40 ± 2.20, a mean DIS score of 12.82 ± 1.29, a mean ID score of 13.71 ± 1.52 and a mean TDI score of 36.93 ± 2.40.

Comparison of the olfactory scores revealed that THR scores were significantly lower on day 90 (8.0 ± 2.51) compared to baseline score (10.4 ± 2.20) ($p = 0.014$). Six months after chemotherapy olfactory threshold function had recovered almost completely (9.65 ± 3.26) (see Fig. 1). In addition, also TDI score decreased non-significantly under chemotherapy (day 0: TDI 36.93 ± 2.4 vs. day 42: TDI 35.69 ± 2.36)) and recovered after completion of therapy (day 180: TDI 36.76 ± 3.42). Odor identification and discrimination tests did not demonstrate significant changes over the study period (Table 2).

Ratings

At baseline examination, 16 patients rated their olfactory function as normal or better than normal. One patient reported about an impaired sense of smell. At follow-up examination on day 42 four patients and on day 90 one patient indicated an impaired sense of smell. At day 180 no patient indicated any impairment in the sense of smell.

At baseline 2 patients reported parosmia resp. 1 patient phantosmia. During the follow-up parosmia increased to 5 patients on day 42, whereas phantosmia remained almost stable. Regarding day 180 parosmia and phantosmia were on the baseline level ($n = 1$ resp. $n = 0$) again.

Beck depression inventory

Patients achieved an average BDI score of 5 ± 6.3 at day 0. The BDI score tended to increase on day 42 (7 ± 5.01) (Fig. 2).

Regarding the correlation between the depressive symptoms and olfactory function, a significant correlation between the BDI and TDI score was only seen on day 180 ($p = 0.007$). The subtest scores (THR, DIS, ID) did not correlate significantly with the BDI score.

Discussion

The aim of the present study was to evaluate olfactory function of testicular cancer patients before, during and 6 months after platinum based chemotherapy by means of

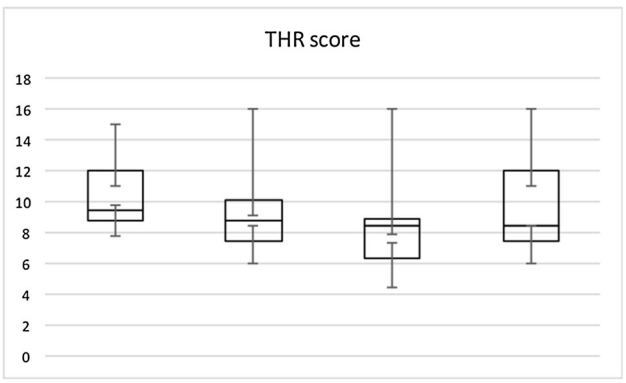

Fig. 1 THR scores from day 0 until day 180 (from the left: day 0, day 42, day 90 and day 180)

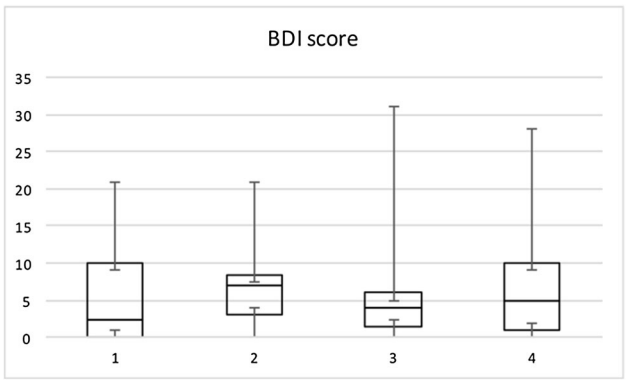

Fig. 2 BDI score on day 0 until day 180 (from the left starting with day 0, day 42, day 90 and day 180)

the validated and widely used Sniffin' Sticks test [23]. As one major result of the present study it could be demonstrated that olfactory sensitivity decreases significantly under chemotherapy which is expressed as a significant increase in the odor threshold test at day 42 (Fig. 1; Table 2). Furthermore, a trend of decrease in TDI score could be seen. These findings are in accordance with Haxel et al., who enrolled 33 patients with malignancies in the head and neck region undergoing chemotherapy (*cis*-, carboplatin, 5-fluoruracil and docetaxel) for evaluation of the sense of smell. They could demonstrate a significant decrease in TDI score during the chemotherapy [8]. In addition, in a cohort of 87 cancer patients (breast cancer or gynecologic malignancies) undergoing various chemotherapy regimens (27% of those platinum containing) it could be demonstrated that olfactory function decreased significantly during chemotherapy but recovered almost completely after termination of the therapy [13]. These results were reaffirmed by a following study investigating 12 ovarian cancer patients receiving carboplatin containing chemotherapy [12]. In accordance with our results, in both studies [11, 12] odor identification of patients undergoing chemotherapy was hardly affected, whereas odor threshold score significantly decreased. These results were confirmed by other research investigating olfactory function of patients undergoing cisplatin containing chemotherapy protocols, that showed odor ID unaffected [7, 13].

However, the present study could show that olfactory sensitivity normalizes after completion of chemotherapy. A trend of improvement of THR and TDI scores was seen 6 months after chemotherapy (Table 1; Fig. 1). All patients presented a normal olfactory function after completing therapy. These results were confirmed by other studies [8, 11, 12]. This is not surprising as olfactory sensory cells are unique among the sensory cells of humans because they are capable for renewing.

Table 1 Clinical staging of included patients according to the TNM classification

Stadium	Number of patients, $n = 17$
CSIA	0
CSIB	7
CSIS	1
CSII	1
CSIIA	3
CSIIB	3
CSIIC	1
CSIII	1
CSIIIA	0
CSIIIB	0
CSIIIC	0

In contrast to the studies who demonstrated olfactory function affected by chemotherapy, other studies did not find any significant difference in psychophysically measured odor threshold scores of cancer patients receiving cisplatin or etoposide based chemotherapy regimens [7, 9]. However, they demonstrated that subjective pleasantness for food odors decreased [7]. Interview-based studies could extend these findings to the sense of smell, as patients reported a decreased olfactory function during chemotherapy [2–4]. In accordance with these results also in the present study patients reported an impaired olfactory function during chemotherapy. Regarding parosmia and phantosmia we found a trend of increasing parosmia during therapy. This was not found for phantosmia, which might be due to the relatively small number of evaluated patients. Nevertheless, humans are quite poor at rating their subjective olfactory acuity [5].

Olfactory dysfunctions are known to negatively influence pleasantness of eating and be associated with taste disturbances [15, 16, 18]. This may be particularly interesting in cancer patients, as this can result in reduced oral intake of food, which can support a decline in patient's nutrition and in consequence patients' quality of life. In line with this, research has recently shown that daily life of oesophagogastric cancer patients undergoing chemotherapy was impacted significantly when food-related changes were experienced [6].

In accordance to this, in this study a significant correlation was found between depressive symptoms and the TDI score after termination of chemotherapy (day 180). This is in line with other studies which demonstrated that olfactory impaired patients typically show signs of depression [26–30] (Tables 2, 3).

The other way around, in a study of 518 cancer patients during chemotherapy, subjects reporting depressed mood were found to suffer more frequently from chemosensory changes during their chemotherapy [2]. In the studied population almost every fourth patient demonstrated a depressed mood after perceiving the diagnosis of testicular cancer. To conclude it is important to screen patients undergoing chemotherapy thoroughly for olfactory impairment to be able to better support them with matching food/diets and offering psychooncological support.

Conclusion

Patients undergoing cisplatin-based chemotherapy for germ cell tumors should be informed about possible transient olfactory impairment during/immediately after chemotherapy.

Table 2 Mean olfactory score obtained before, during and after chemotherapy

	THR score (mean ± SD)	DIS score (mean ± SD)	ID score (mean ± SD)	TDI score (mean ± SD)
Day 0	10.4 ± 2.20	12.82 ± 1.33	13.71 ± 1.53	36.93 ± 2.40
Day 42	9.10 ± 2.31	12.59 ± 1.33	14.0 ± 1.08	35.69 ± 2.36
Day 90	8.0 ± 2.51	13.24 ± 1.48	13.94 ± 1.61	35.18 ± 2.95
Day 180	9.65 ± 3.26	13.06 ± 1.66	14.06 ± 1.0	36.76 ± 3.42

Table 3 Subjective rating of olfactory function before, during and after chemotherapy

	Day 0 (n = patients)	Day 42 (n = patients)	Day 90 (n = patients)	Day 180 (n = patients)
Olfactory function −1	1	4	1	0
Olfactory function 0	14	9	12	15
Olfactory function 1	2	4	3	1
Olfactory function 2	0	0	1	1

Olfactory function 0 = rated normal, −1 = rated worse than normal, 1 = olfaction rated better than normal, 2 = excellent olfaction

Support of the patients by matching food and diets should be taken into consideration.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. Siegel R, Ward E, Brawley O, Jemal A (2011) Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 61:212–236. doi:10.3322/caac.20121
2. Bernhardson B-M, Tishelman C, Rutqvist LE (2007) Chemosensory changes experienced by patients undergoing cancer chemotherapy: a qualitative interview study. J Pain Symptom Manage 34:403–412. doi:10.1016/j.jpainsymman.2006.12.010
3. Hong JH, Omur-Ozbek P, Stanek BT et al (2009) Taste and odor abnormalities in cancer patients. J Support Oncol 7:58–65
4. Rhodes VA, McDaniel RW, Hanson B et al (1994) Sensory perception of patients on selected antineoplastic chemotherapy protocols. Cancer Nurs 17:45–51
5. Philpott CM, Wolstenholme CR, Goodenough PC et al (2006) Comparison of subjective perception with objective measurement of olfaction. Otolaryngol Head Neck Surg 134:488–490. doi:10.1016/j.otohns.2005.10.041
6. de Vries YC, Helmich E, Karsten MDA et al (2016) The impact of chemosensory and food-related changes in patients with advanced oesophagogastric cancer treated with capecitabine and oxaliplatin: a qualitative study. Support Care Cancer 24:3119–3126. doi:10.1007/s00520-016-3128-z
7. Joussain P, Giboreau A, Fontas M et al (2013) Cisplatin chemotherapy induces odor perception changes in bronchial cancer patients. Lung Cancer 82:168–170. doi:10.1016/j.lungcan.2013.06.009
8. Haxel BR, Berg S, Boessert P et al (2016) Olfaction in chemotherapy for head and neck malignancies. Auris Nasus Larynx 43:74–78. doi:10.1016/j.anl.2015.07.004
9. Ovesen L, Sørensen M, Hannibal J, Allingstrup L (1991) Electrical taste detection thresholds and chemical smell detection thresholds in patients with cancer. Cancer 68:2260–2265
10. Riga M, Chelis L, Papazi T et al (2015) Hyposmia: an underestimated and frequent adverse effect of chemotherapy. Support Care Cancer 23:3053–3058. doi:10.1007/s00520-015-2675-z
11. Steinbach S, Hummel T, Böhner C et al (2009) Qualitative and quantitative assessment of taste and smell changes in patients undergoing chemotherapy for breast cancer or gynecologic malignancies. J Clin Oncol 27:1899–1905. doi:10.1200/JCO.2008.19.2690
12. Steinbach S, Hundt W, Schmalfeldt B et al (2012) Effect of platinum-containing chemotherapy on olfactory, gustatory, and hearing function in ovarian cancer patients. Arch Gynecol Obstet 286:473–480. doi:10.1007/s00404-012-2307-5
13. Yakirevitch A, Talmi YP, Baram Y et al (2005) Effects of cisplatin on olfactory function in cancer patients. Br J Cancer 92:1611–1613. doi:10.1038/sj.bjc.6602544
14. Gietema JA J, Renken RJ, Gietema JA et al (2016) Taste and smell function in testicular cancer survivors treated with cisplatin-based chemotherapy in relation to dietary intake, food preference, and body composition. Appetite 105:392–399. doi:10.1016/j.appet.2016.06.010
15. Brisbois TD, Hutton JL, Baracos VE, Wismer WV (2006) Taste and smell abnormalities as an independent cause of failure of food intake in patients with advanced cancer—an argument for the application of sensory science. J Palliat Care 22:111–114
16. Hutton JL, Baracos VE, Wismer WV (2007) Chemosensory dysfunction is a primary factor in the evolution of declining nutritional status and quality of life in patients with advanced cancer. J Pain Symptom Manag 33:156–165. doi:10.1016/j.jpainsymman.2006.07.017
17. Merkonidis C, Grosse F, Ninh T et al (2015) Characteristics of chemosensory disorders—results from a survey. Eur Arch Otorhinolaryngol 272:1403–1416. doi:10.1007/s00405-014-3210-4
18. Tisdale MJ (2001) Cancer anorexia and cachexia. Nutrition 17:438–442
19. Hummel T, Nordin S (2005) Olfactory disorders and their consequences for quality of life. Acta Otolaryngol 125:116–121

20. Shu CH, Lee PO, Lan MY, Lee YL (2011) Factors affecting the impact of olfactory loss on the quality of life and emotional coping ability. Rhinology 49:337–341. doi:10.4193/Rhino10.130
21. Smeets MAM, Veldhuizen MG, Galle S et al (2009) Sense of smell disorder and health-related quality of life. Rehabil Psychol 54:404–412. doi:10.1037/a0017502
22. Schiffman SS, Sattely-Miller EA, Taylor EL et al (2007) Combination of flavor enhancement and chemosensory education improves nutritional status in older cancer patients. J Nutr Health Aging 11:439–454
23. Hummel T, Sekinger B, Wolf SR et al (1997) "Sniffin" Sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 22:39–52
24. Kobal G, Hummel T, Sekinger B et al (1996) "Sniffin' Sticks": screening of olfactory performance. Rhinology 34:222–226
25. Beck AT, Ward CH, Mendelson M et al (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571
26. Hautzinger M, Bailer M, Worall HFK (1995) Beck-Depressions-Inventar (BDI). Testhandbuch. Hans Huber, Bern
27. Jung YG, Lee J-S, Park GC (2014) Does post-infectious olfactory loss affect mood more severely than chronic sinusitis with olfactory loss? Laryngoscope 124:2456–2460. doi:10.1002/lary.24691
28. Miwa T, Furukawa M, Tsukatani T et al (2001) Impact of olfactory impairment on quality of life and disability. Arch Otolaryngol Head Neck Surg 127:497–503
29. Temmel AFP, Quint C, Schickinger-Fischer B et al (2002) Characteristics of olfactory disorders in relation to major causes of olfactory loss. Arch Otolaryngol Head Neck Surg 128:635–641
30. Kohli P, Soler ZM, Nguyen SA et al (2016) The association between olfaction and depression: a systematic review. Chem Senses 41:479–486. doi:10.1093/chemse/bjw061