Short Communication

Effects of cisplatin on olfactory function in cancer patients

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A prospective analysis of olfaction was performed in 21 patients receiving cisplatin. A reduction in olfactory function was noted in only one patient. Hearing impairment was documented in nine patients, none of whom had impaired sense of smell. We conclude that cisplatin has no major deleterious effect on olfactory function at doses which cause hearing impairment.

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Methods

Olfactory function was tested before beginning chemotherapy (baseline), and after each course of cisplatin. The final olfactory assessment was performed at least 3 weeks after the last course of cisplatin.

Olfaction was assessed using the ‘Sniffin’ Sticks® kit consisting of odorants in felt-tip pens (Wolfensberger et al, 2000). For odour presentation, the opened pens are positioned approximately 2 cm in front of both nostrils (all patients were tested bilaterally) for 3–4 s at intervals of 30 s. A patient has to choose one of four items that best describes the presented odour. The number of correctly chosen items gives the olfactory status score.

The sign test and Wilcoxon signed rank test for matched samples were used to estimate the statistical significance of the

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changes. The Spearman rank correlation was calculated for estimation of the relationship between the changes and the number of measurements.

Standard audiometry monitoring was performed. Serum zinc levels were measured in 14 patients.

RESULTS

In all, 21 patients completed the planned chemotherapeutic treatment. They received one to six (mean 3.4) cycles of chemotherapy, with cumulative doses of cisplatin ranging from 180 to 945 mg and a mean cumulative dose of 525 mg (330 mg m$^{-2}$). In one patient, a 60% decrease in olfaction was noted after the third course of treatment and a cumulative dose of cisplatin of 225 mg m$^{-2}$. No decrease in olfactory function was found in 20 (95.3%) patients and in fact 10 patients had a final olfaction score that was higher than the pretreatment score. These score changes were statistically significant ($P = 0.0117$ for the sign test and $P = 0.0322$ for the Wilcoxon test). However, the rank correlation between the number of measurements and the improvement in olfactory function in these patients (rho = 0.505, $P = 0.014$) suggests that this may be a result of learning effect.

Hearing impairment was documented in nine patients (bilateral high tone sensori-neural hearing loss in all cases). The single patient whose olfactory function decreased had no hearing loss. Of 14 patients whose serum zinc levels were analysed, it was normal or increased in 12, according to normal ranges (75–120 mcg dl$^{-1}$). In two patients reduced levels of zinc were seen after the second and third chemotherapeutic course, respectively. Neither of these patients had impaired olfaction. In one of them hearing impairment was registered. The patient whose olfactory function deteriorated had normal serum zinc levels.

DISCUSSION

Cisplatin-induced olfactory deterioration is a possible consequence of the recognised neurotoxicity of this agent (Bartoshuk, 1995; Comeau et al, 2001; Peltier and Russell, 2002). An additional factor that could aggravate this effect is zinc deficiency, which has been found to be associated with taste dysfunction (Heyneman, 1996). The specific role of zinc in the control of taste and smell is unknown, but it is functionally involved at several levels of cellular organisation (Ripamonti et al, 1998). Cisplatin has been reported to increase urinary zinc excretion and reduce serum zinc levels (Sweeney et al, 1989). Oral zinc administration has been shown to hasten recovery of the sense of taste in patients undergoing radiotherapy for head and neck cancer (Ripamonti et al, 1998). It was therefore suggested that cisplatin might impair olfaction not only by its neurotoxic effect, but also indirectly via depletion of serum zinc levels.

Until recently, it was difficult to accurately measure olfactory status due to a lack of accurate and reproducible tools. ‘Sniffin’ sticks® kit used allows assessment of odour differentiation acuity rather than olfactory thresholds evaluation. Minimal and maximal limits of olfactory performance measured with this kit do not allow recording of further improvement of olfactory function in patients with maximal score or further deterioration in patients with minimal score. The fact that in 10 of 21 patients the final olfaction score was higher than the pretreatment score can possibly be explained by the patients learning the odours used in the test over time. The rank correlation between the number of measurements and the improvement in measured olfaction supports the contention that this may be a result of learning effect. Despite these limitations to our study, the lack of a decrease in olfactory function in all 10 patients who developed cisplatin-induced hearing reduction indicates that cisplatin has no significant deleterious effect on olfactory function.

CONCLUSIONS

Though subjective olfactory function impairment has been reported by a considerable number of cisplatin-treated patients (Rhodes et al, 1994; de Graeff et al, 2000), the only objective study thus far failed to show such an effect. Ovesen measured olfactory thresholds in 22 patients prior to and 2–3 months after treatment with several chemotherapeutic agents. They did not find statistically significant changes in olfaction although it should be noted that in this study the testing was performed with binary dilutions of a single odorant (Ovesen et al, 1991).

The results of our study performed with a more sophisticated test of olfactory function confirm the lack of an early effect of cisplatin on olfactory function. A decrease in olfaction was noted in one patient (4.7%) in our study. The cumulative dose of cisplatin given to this patient was relatively low and chemotherapy was discontinued after three cycles because of disease progression. Our results are in accordance with the results of Ovesen et al, who also failed to demonstrate impaired olfaction following treatment with cisplatin. A quality-of-life questionnaire-based study reported a subjective change in sense of smell in 26% of patients following high-dose chemotherapy and bone marrow transplantation, although more patients reported an increase in smell sensation rather than a decrease (Epstein et al, 2002).

In our study, the incidence of hearing impairment, an accepted indicator of cisplatin neurotoxicity, was 48%, which is comparable with results of similar studies (Blakley and Myers, 1993). The single patient whose olfactory status did deteriorate had no detectable hearing impairment. Serum zinc levels were monitored in 14 (67%) patients in the study. Only two (12%) of them showed a tendency toward hypozincæmia. The single patient with impaired olfaction had normal zinc levels after cisplatin treatment.

Our study has several limitations. It is a single-blind study and did not include a control group of patients who were not receiving cisplatin through the comparable period of the study. The ‘Sniffin’ sticks® kit used allows assessment of odour differentiation acuity rather than olfactory thresholds evaluation. Minimal and maximal limits of olfactory performance measured with this kit do not allow recording of further improvement of olfactory function in patients with maximal score or further deterioration in patients with minimal score. The fact that in 10 of 21 patients the final olfaction score was higher than the pretreatment score can possibly be explained by the patients learning the odours used in the test over time. The rank correlation between the number of measurements and the improvement in measured olfaction supports the contention that this may be a result of learning effect. Despite these limitations to our study, the lack of a decrease in olfactory function in all 10 patients who developed cisplatin-induced hearing reduction indicates that cisplatin has no significant deleterious effect on olfactory function.

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