Theses of Doctoral (Ph.D.) Dissertation

DETECTION OF OTOTOXIC EFFECT IN TESTICULAR CANCER PATIENTS WITH OTOACUSTIC EMISSION

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INTRODUCTION

Testicular germ cell cancer is one of the most frequent malignancies among young males with incidence rates still on the increase. The prognosis of testicular germ cell tumors was dramatically improved by the introduction of cisplatin. Cisplatin is one of the most potent cytotoxic drugs currently available for cancer chemotherapy, and is especially effective in the treatment of testicular cancer. (More than 80% of our testicular cancer patients are cured, and we follow up on them through their lifespan). The efficacy of cisplatin, however, is limited by severe side effects, which include renal injury, peripheral neuropathies, hearing impairment, nausea, vomiting, and myelosuppression. Of these, peripheral neurotoxicity and ototoxicity are potentially the major dose-limiting factors, in that they are cumulative and in general only partially reversible with discontinuation of therapy. In the last 25 years there were several significant discoveries in hearing research. Probably the most important was the discovery of otoacoustic emission by David Kemp in 1978. It has been shown by Kemp that during the physiologic amplification of sound, the inner ear produces mechanical vibrational energy (otoacoustic emission) which can travel retrogradely through the middle ear canal and can be recorded there. If the middle-ear function is normal the amplitude of this energy reflects the functional status of inner ear. Kemp has produced a simple instrument for detecting click-evoked otoacoustic emissions, and it has been proven to be a valuable tool for the assessment of hearing not requiring the reactions of patient or sound-isolated room. Since the
inner ear is the most vulnerable part of hearing (either to toxic effect or noise) it is reasonable to postulate that these effects may be ideally monitored by otoacoustic emission. Hearing loss affects millions of people worldwide and finding an objective and quick method for early detection and follow up, has been a priority for researchers for a long time. Such a method would enable clinicians to make rational decisions regarding the modification of treatment protocols with cisplatin. The aim of this study was to analyze the incidence, the characteristics and risk factors of cisplatin induced ototoxicity in testicular cancer patients, detected by different type of otoacoustic emissions.
AIMS OF THE STUDY

1. To determine whether the administration of 20mg/m² body surface cisplatin daily (in combination with other antitumor drugs) for 5 days alters the amplitude of TOAE (transient otoacoustic emission), detected on the fifth day of chemotherapy. (early ototoxic effect)

2. To determine whether our cisplatin containing protocols alter the amplitude of DPOAE (distorsion product otoacoustic emission) month or years after treatment (late ototoxic effect).
   2.1. To determine the prevalence of hearing loss
   2.2. To study the relationship between cisplatin dose and hearing loss.
   2.3. To determine the risk factors contributing to hearing loss

3. To compare the prevalence of SOAE (spontaneous otoacoustic emission) between the treated and control groups.

4. To study the advantages and disadvantages of the different types of otoacoustic emissions as screening method.
PATIENTS AND METHODS

1. Early ototoxic effect:
1.1. Study protocol
Before chemotherapy (1. day)
- Informed consent
- Medical history
- Otoscopic exam of the outer ear canal followed by a tympanometry test to exclude any conductive component
- Conventional audiometry
- Detection of TOAE.
- Recording data for statistical evaluation (Excel table)

After chemotherapy (5. day)
- Evaluating subjective complains
- Otoscopic exam.
- Tympanometry.
- Conventional audiometry.
- TOAE
- Recording data for statistical evaluation.

1.2 Inclusion criteria
- Testicular cancer patients treated at the Chemotherapy-C and Clinical Pharmacology Department of the National Institute of Oncology, who didn’t receive chemotherapy earlier.
- Patients under 55 (to avoid presbyacusis)
- Unblocked outer ear canal.
- „A” type tympanogram
• Patients with a near normal hearing threshold (hearing loss smaller than 20 dB HL at 0.5 and 1.2 kHz)
• Patients with a reproducible TOAE (Repro> 80%).
• Patients who gave their consent to be included in the study

1.3. Study groups:
1. Group 1: 10 males (20 ears) with different histological types of testicular germ cell tumors (age 22-39 mean 27).
2. Group 2: 10 healthy control persons (without therapy) matching sex age distribution and measurement set up of group 1.

1.4. Statistical evaluation:
Paired “t”, independent “t” and Wilcoxon tests were used for statistical evaluation. Significance was accepted at the p≤0.05. The results from the left and right ears were treated as independent data.

2. Late ototoxic effect:
2.1. Study protocol
• Informed consent
• Medical history
• Otoscopic exam of the outer ear canal followed by a
• tympanometry test to exclude any conductive component
• Detection of DPOAE.
• Detection of SOAE
• Recording data for statistical evaluation (Excel table)

2.2. Inclusion criteria
• Testicular cancer patients who were treated at the Chemotherapy-C and Clinical Pharmacology Department of the National Institute of Oncology, month or years before the study. (treated group)
• Testicular cancer patients who didn’t receive chemotherapy (control group)
• Minimum follow up time of 6 month after the last cycle of chemotherapy (in the treated group).
• Patients under 55 (to avoid presbyacusis)
• Unblocked outer ear canal.
• „A” type tympanogram
• Patients who gave their consent to be included in the study

2.3. Study groups
223 patient- out of 273 measured- met the inclusion criteria. These 223 testicular cancer patients (with different histological types of testicular germ cell tumor) median follow up time of 4.27 years (range 0,5- 20 years) and a median age of 37 years (range 18-55 years) were assessed by DPOAE. 100mg/m² cisplatin (20mg/m² daily for five days) were administered per cycle, in EP, BEP, VeIP, VIP or VPB regimens. Cisplatin was administered for 60 minutes with pre- and posthydration. (total
volume:2500ml) Familial hearing loss (N=0), chronic otitis media (N=0), head injuries (3 cases) was negligible. The control group consisted of 40 (out of 49 measured) testicular cancer patients without chemotherapy, median age 35 years (range 16-54 years).

2.4. Statistical evaluation: Paired t-test and Mann-Whitney test were used for statistical evaluation. We did both test for every statistical analysis. Since the distribution was normal, no significant differences were detected between the results of the two tests. As multiply testing were performed significance was accepted at the p≤0.01. The results from the left and right ears were treated as independent data. We also carried out stepwise discriminant analysis, to evaluate the factors with predictive value for hearing loss. For statistical analysis, patients were stratified to subgroups of cumulative dose of cisplatin, symptomatic complaints, and risk factors as smokers or non-smokers and former noise exposure.

RESULTS

1 Early ototoxic effect:

TOAE (transient otoacoustic emission)

1. The prevalence of TOAE was 100% when audiometric threshold was normal.
2. TOAE measurement took two minutes per subject.
3. No differences were found either in otological physiological examinations or in conventional audiometry and tympanometry (threshold change smaller than 10dB HL) before and after therapy.

4. There were no statistically significant differences in amplitude either before and after therapy or between patient and control groups. (Statistical evaluations were carried out with “t” and Wilcoxon tests)

5. In the treated group from the 20 ears: in 2 the amplitude didn’t change, in 11 it decreased and in 7 increased. The average of the differences was 0.25 dB. The difference wasn’t statistically significant. (p=0.32 with “t” probe and p=0.33 with Wilcoxon probe)

6. In group 1, there were 2 patients with (possibly noise induced) high-frequency hearing loss; that didn’t change after therapy.

7. No patients complained of hearing loss or tinnitus.

2. Late ototoxic effect:

2.1. DPOAE (distorsion otoacoustic emission)

Amplitude changes on different dose levels: We compared the treated group and the control group on every dose level. In patients receiving at most 300mg/m² cisplatin (1-3 cycles) no significant amplitude changes were detected. Beyond this dose hearing impairment proved to be dose-dependent. Contrary to the literature,
not only high frequencies were affected. In patients receiving at least 400mg/m² our method could detect significant hearing impairment at lower frequencies that are important for speech perception. At 400mg/m² significant amplitude change was detected at 3000Hz and 4000Hz (p=0.0105, 0.0005) at 500-600mg/m² significant amplitude change was detected at 1500Hz, 2000Hz, 3000Hz, 4000 Hz and 8000 Hz (p=0.0045; 0.0001; 0.0002; 0.0006; 0.0028), at 700mg/m² and above significant amplitude change was detected at 3000 Hz, 4000 Hz, 6000 Hz and 8000 Hz (p=0.014, 0.0046; 0.0004; 0.0007). We detected the worst hearing at those 44 patients who had symptomatic ototoxicity. They had significant hearing impairment on all frequencies from 1000Hz to 8000Hz (p=0.00)

2.2. SOAE (spontaneous otoacoustic emission)

There were no statistically significant differences in the incidence of SOAE, between the treated and the control group. The prevalence of SOAE among our patients was somewhat lower than the normal value in the literature for males. In the control group the SOAE incidence was 28.3%, in patients with 1-3 cycles of cisplatin it was 25.9%, and in patients with 4 or more cycles it was 24.6%
2.3. Subjective symptoms:

44 (20%) patients reported symptoms, either tinnitus 32 (15%) or hearing loss 7 (3%), 5 (2%) patients reported both. 177 patients did not have any ototoxic symptoms, and 2 patients didn’t fill out the questionnaire. Symptomatic patients received higher doses of CDDDP (4.37 cycles versus 3.83) though the difference was not significant. (p=0.06).

2.4. Risk factors:

In the treated group the only statistically significant risk factor for hearing loss was the cumulative dose of cisplatin; neither smoking nor noise exposure were independent risk factors. There were no significant differences between the cumulative dose of the smokers and the non-smokers, the noise injured and not injured, so we compared these groups as a whole. We did not find any significant differences in amplitudes between these groups.

In the control group we made the same comparison between the smokers and non-smokers and the noise injured and not injured. In this group noise exposure was significant predictor for hearing impairment. We found significant difference between the noise injured and not injured at 4000Hz, 6000Hz and 8000Hz.
We also carried out stepwise discriminant analysis, with age, cumulative dose of cisplatin, smoking and noise exposure. The analysis revealed that only age and cumulative dose of cisplatin are independent prognostic factors for hearing loss. Their cumulative effect is altogether 62.9%. Noise and smoking has no predictive value at all.
CONCLUSIONS, NEW FINDINGS

1. Both TOAE and DPOAE are fast, noninvasive, and reliable method in detecting and follow up ototoxicity in testicular cancer patients.

2. The advantage of TOAE is in its speed, DPOAE allow greater frequency specificity and can be used to record at higher frequencies than TOAE. Neither of them needs sound-proof chamber or specific staff.

3. Since the prevalence of SOAE in our study was less than 30%, its relevance and clinical use remained uncertain.

4. In the acute phase study no differences were found either in otological physiological examinations or in conventional audiometry and tympanometry before and after therapy. Similarly there were no statistically significant differences in amplitude either before and after therapy or between patient and control groups.

No patients complained of hearing loss or tinnitus.

5. Since our results did not show any significant amplitude change after 20mg/m² cisplatin daily for 5 days, in contrast with other studies that described broad frequency reduction of the emission amplitude in 30-86% of cases, treated with 100mg/m² of cisplatin for 1 day, we suggested that between the similarly effective regimens those containing lower daily cisplatin doses should be used.
6. In our study for late ototoxicity, contrary to the literature, not only high frequencies were affected. In patients receiving at least 400mg/m² our method could detect significant hearing impairment at lower frequencies that are important for speech perception (1000-3000Hz).

7. 44 (20%) patients reported symptoms, either tinnitus and/or hearing loss. We detected the worst hearing at these 44 patients.

8. Since hearing loss contributes to the already compromised situation of cancer patient, testicular cancer patients undergoing chemotherapy should have their hearing monitored regularly. Cisplatin in adequate doses has to be applied in order to cure a testicular cancer patient, but as hearing loss correlates with the cumulative dose of cisplatin, doses of chemotherapy should be reduced to the minimum required for cure.
SUMMARY

The aim of the research was to detect the acute and long-term ototoxic effect of cisplatin in testicular cancer patients, using OAE (otoacoustic emission), a highly sensitive new objective method, for detecting medication-related hearing loss. Secondary objective was to evaluate the risk factors that contribute to hearing loss. In the study for acute hearing loss ten males with different histological types of testicular germ cell tumor were examined with TOAE, (transiently evoked otoacoustic emission), before the 1st and after the 5th day of their 1st cycle of cytostatic therapy. 100 mg/m2 cisplatin were administered per cycle, (20mg/m2 for five days). Ten age-matched healthy volunteers of good hearing and without treatment were also examined with the same method. Wilcoxon and paired t-tests were used for statistical evaluation. In this acute phase study no differences were found either in otological physiological examination or in conventional audiometry, or in tympanometry. There were no statistically significant differences in amplitude either before and after therapy, or between patient and control group. No patient complained of hearing loss or tinnitus. In the long term hearing loss study 223 cured patients were assessed by DPOAE (distorsion product otoacoustic emission) 100mg/m2 cisplatin were administered per cycle, in EP, BEP, VeIP, VIP or VPB regimens. The control group consisted of 40 testicular cancer patients without chemotherapy. A detailed medical history of the patient
and his family evaluated audiological risk factors and hearing complaints. Before DPOAE, otoscopic examination and tympanometry tests were used to exclude any conductive component. DPOAE was measured in eight frequencies from 750 to 8,000 Hz. Paired t-test, Mann-Whitney test and stepwise discriminant analysis were used for statistical evaluation. Symptomatic ototoxicity was observed in 20% of the patients. In patients receiving \(<=300\) mg/m² cisplatin, no amplitude changes were detected. Beyond this dose, hearing impairment proved to be dose dependent. Contrary to the literature, not only high frequencies were affected. In patients receiving \(>=400\) mg/m², our method could also detect significant hearing impairment at lower frequencies that are important for speech perception. (1000-3000Hz). The lowest amplitudes were detected in those patients who had symptomatic ototoxicity. The only statistically significant risk factors were the cumulative dose of cisplatin and age; neither smoking nor previous noise exposure proved to be risk factors. As the life expectancy of testicular cancer patients matches in most cases the life expectancy of healthy males, studying long-term side effects is of great importance. OAE is a fast, noninvasive and reliable method in detecting ototoxicity in testicular cancer patients. Cisplatin dose regimens should be reduced to the minimum required for cure, based on a risk-adapted treatment.
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