http://dx.doi.org/10.23925/2176-2724.2017v29i3p438-447

Auditory monitoring in adults undergoing chemotherapy with carboplatin

Monitoramento auditivo em adultos submetidos à quimioterapia com carboplatina

Monitoreo del oído en adultos sometidos a quimioterapia con carboplatino

Priscila Ivanchuk Damian[*]
Tatiane Almeida Valverde[*]
Daiane Pereira Guimarães[*]
Daniela Gil[*]

Abstract

Purpose: To characterize the hearing of adult patients undergoing chemotherapy with carboplatin using two sequential audiological tests during chemotherapy treatment. **Methods**: Prospective and observational. The participants were six adult subjects between 53 and 59 years and 11 months, undergoing chemotherapy treatment with carboplatin subjected to a battery of audiological exams. Data were analyzed using the ANOVA test, z test for proportions and Wilcoxon signed-ranks test. The adopted significance was 5% ($p \leq 0.05$). **Results**: An increase in hearing thresholds was observed, particularly in the higher frequencies, but there was no significance. It was also observed an increase in the signal / noise ratio of transient evoked otoacoustic emissions and for distortion product, but without statistical significance. **Conclusion**: No statistically significant changes regarding the hearing thresholds and responses of otoacoustic emissions were observed, however it could be noted an increase in hearing thresholds, especially at high frequencies, as well as the increased amplitude on the responses in otoacoustic emissions.

Keywords: Hearing loss; Audiometry; Hearing loss; Carboplatin; Toxicity.

Oral presentation at the 31º Encontro Internacional de Audiologia - EIA, on May 28th, 2016, in São Paulo - SP, Brazil.
* Universidade Federal de São Paulo, São Paulo, SP, Brazil.
Authors' contributions:
PID: Project elaboration, recruitment of volunteers, conducting examinations, results analysis, writing, submission and paperwork.
TAV: Recruitment of volunteers, conducting examinations, results analysis.
DPG: Correction of research project, recruitment of volunteers, correction of article writing.
DG: Adviser, preparation and correction of the research project, ethics procedures in research, supervision of the examinations, analysis of results, correction of the writing of the article and approval of the final version.

Correspondence address: Priscila Ivanchuk Damian priscila.ivanchuk@gmail.com
Received: 09/12/2016
Accepted: 16/09/2017

Resumo

Objetivo: Caracterizar a audição de pacientes adultos submetidos à quimioterapia com carboplatina por meio de exames audiológicos em dois momentos durante o tratamento quimioterápico. **Métodos**: Prospectivo e observacional. Participaram da pesquisa seis sujeitos adultos entre 53 e 59 anos e 11 meses, em tratamento quimioterápico com carboplatina submetidos a uma bateria de exames audiológicos. Os dados foram analisados por meio do teste ANOVA, teste z para proporções e Teste de Wilcoxon. O valor de significância adotado foi de 5% (p≤0,05). **Resultados**: Um aumento nos limiares auditivos foi observado, sobretudo nas frequências mais altas, porém não houve significância. Também foi observado aumento na relação sinal/ruído das emissões otoacústicas evocadas transientes e por produto de distorção, porém sem significância estatística. **Conclusão**: Não foram observadas mudanças estatisticamente significantes quanto aos limiares auditivos e as respostas das emissões otoacústicas, no entanto pode-se notar um aumento nos limiares audíveis, especialmente nas altas frequências, bem como aumento da amplitude de respostas nas emissões otoacústicas.

Palavras-chave: Perda auditiva; Audiometria; Carboplatina; Toxicidade.

Resumen

Objetivo: Caracterizar la audición de pacientes adultos sometidos a quimioterapia con carboplatino a través de pruebas audiológicas dos veces durante la quimioterapia. **Métodos**: Estudio prospectivo observacional. Los participantes fueron seis sujetos adultos de entre 53 y 59 años y 11 meses, sometidos a quimioterapia con carboplatino sometido a una batería de pruebas audiológicas. Los datos se analizaron mediante la prueba de ANOVA, prueba z para proporciones y prueba de los rangos con signo de Wilcoxon. La significancia fue del 5% (p ≤ 0,05). **Resultados**: fueron observados un aumento de los umbrales de audición, en particular en las frecuencias más altas, pero no identificaron significación. También se observó un aumento de la relación señal / ruido de emisiones otoacústicas evocadas transitorias y productos de distorsión, pero sin significación estadística. **Conclusión**: Los cambios estadísticamente significativos con respecto a los umbrales de audición y las respuestas de las emisiones otoacústicas, fueron observadas sin embargo es posible que observe un aumento de los umbrales audibles, especialmente a altas frecuencias, así como una mayor gama de respuestas de las emisiones otoacústicas.

Palabras clave: Pérdida auditiva; Audiometría; Carboplatino; Toxicidad.

Introduction

The hearing losses can presente several etiologies. One of the possible causes of changes in the hearing tresholds is the use of ototoxic medicines, such as antibiotics, loop diuretics and some antineoplastics. These medicines may cause lesions in the hair cells of the Corti organ, in the vestibular cells and hearing structures of the brainstem, resulting in transitory and/or permanent disturbances of the hearing according to the characteristic of each drug [1, 2]. The hearing loss induced by the use of antineoplastics is usually characterized for being bilateral, symmetrical and sensorural, being definitive and irreversible. [3].

Among the most used antineoplastics there is carboplatin (Platamine® CS, manufacturer Pfizer, Bentley – Australia), which is widely used in chemotherapy treatment of malignant neoplasms such as ovarian carcinomas of advanced epithelial origin, small cell lung carcinomas, squamous cell carcinomas of the head and neck, and also carcinomas of the cervix. The carboplatin is a second generation chemotherapeutic, developed in 1981 from cisplatin, with the aim of being less cytotoxic than the previous one [4]. Studies show that the adverse reaction such as alopecia, gastrotoxicity, nephrotoxicity, ototoxicity, muscle toxicity and tinnitus, resulting from the use of carboplatin were lower than those of cisplatin, with the exception of myelosuppression which is more frequent in patients taking carboplatin [5, 6, 7].

The action of platinum results on cell oxidation, leading to an alkylation process, inhibits the synthesis of DNA from the tumor cell of cross-links between the nitrogenous bases of the same DNA molecule or adjacent molecules, leading to tumor cell to apoptosis (celular death) [7, 8]. A study with

guinea pigs [9] revealed that the cisplatin as much as the carboplatin cause lesions to the tissues by means of cross-links between nucleotides of DNA molecules, resulting to apoptosis, however, this effect was more intense in the groups submited to cisplatin, indicating smaller ototoxic potential of the carpoplatin whe compared to cisplatin. Experimental researches revealed that the ototoxic drugs derived from platinum initialy rush to the cochlea bases, which due to its tonotopia, first reflect the change of hearing tresholds of higher frequency [10, 11] and might also rush to the ganglion, the hearing nerve [12] and the inferior colliculus in the brainstem [13]. Experimental data are important concerning the direction of clinical research, on the top of all about the applicability and hearing monitoring criteria in humans.

In view of the pathophysiology of ototoxic lesions observed in experimental studies, as well as empirically observed in the audiological clinic, the hearing monitoring of patients exposed to ototoxic drugs should include conventional audiometry (250 to 8,000 Hz) and vocal tone, audiometry of high frequencies, immittance measurements, transient stimulus evoked by otoacoustic emissions (TEOAE), distortion product evoked by otoacoustic emissions (DPOAE) and brainstem hearing evoked potential, as indicated by the American Speech-Language-Hearing Association hearing monitoring guidelines (ASHA) published in 1994. ASHA's hearing monitoring guidelines also indicate that counseling is performed prior to the initiation of chemotherapy treatment, in which the patient can be informed of possible fluctuations or hearing changes, tinnitus, changes in balance, sensation of fullness and potentiation when exposed to noise. ASHA recommends that the first hearing evaluation happens a week before the first chemotherapeutic administration or 24 hours after the first drug administration maximum, and that the following evaluations happen 24 hours before the administration of the platinum doses, also it is importante to have hearing evaluations in the third, sixth, ninth and twelfth months after the treatment ends [14].

A research made with 13 people aged between 7 and 20 years old, with osteosarcoma and who were submitted to eight cycles of chemotherapy with cisplatin, has shown increase of hearing tresholds in high frequencies after the first cisplatin administration and that the transient otoacoustic emissions and distortion product tended to increase their amplitude and then to decrease. At the end of treatment all patients had hearing loss at high frequencies[15].

Another study of 32 children who received doses of cisplatin, cisplatin and later carboplatin or carboplatin alone has shown that high frequency audiometry and DPOAE were sensitive to falls in hearing thresholds, which occurred initially at high frequencies [16].

The literature has also shown that individuals treated with ototoxic chemotherapeutics may develop hearing loss after the end of treatment and emphasized the importance of audiological follow-up after chemotherapy [17, 18, 19]. In another study, it was shown that both otorhinolaryngological and audiological care of these patients are uncommon [20].

In view of the results found in literature, it is possible to spot the importance of performing hearing monitoring in patients submitted to chemotherapeutic treatments with ototoxic drugs, aiming at an early diagnosis of hearing threshold disturbances and enabling improvement of the individual's quality of life, since alternative measures of procedures, review of treatment and / or drug dose or even rehabilitation with individual sound amplification apparatus, can be discussed with the medical and multiprofessional teams involved in the treatment of the patient.

Due to the lack of articles with hearing monitoring in adults submitted to ototoxic chemotherapeutic treatments, especially with carboplatin, in literature, this research aimed to characterize the hearing of this population by means of a battery of audiological exams performed at two moments during the chemotherapy treatment.

Methodology

Observational, prospective research. Approved by the Research Ethics Committee of Universidade Federal de São Paulo (UNIFESP) and by the Brazilian Platform, CAAE 33383114.1.0000.5505, opinion no. 726,263. The volunteers received information about the research and signed the Informed Consent Term.

The sample was recruited from the Clinical and Experimental Oncology Center of the Chemotherapy Ambulatory Clinic of Universidade Federal de São Paulo (UNIFESP) and it was composed of six individuals aged 53-59 years and 11 months

old, four of whom were male and two were female. As research criteria the patient should be between 18 to 59 years and 11 months old and be on chemotherapy with carboplatin. The association with other drugs without ototoxic potential was not an exclusion criterion, however, patients who underwent cisplatin chemotherapy concomitantly or had this alteration during the chemotherapy cycles did not enter this sample. Between September 2014 and October 2015, 77 eligible patients for research were selected, six of whom could participate in the two stages of the evaluation. The others could not initiate or complete the two steps for reasons such as: rescheduled chemotherapy at a time that is not compatible with audiological care, unable to travel to the audiology outpatient clinic, fatigue and fragility, withdrawal and / or death.

The audiological tests were performed at two moments during the chemotherapy treatment. All the volunteers had already started the chemotherapy protocol and it was not possible to control at what time of the doses the patient was when he started participating in the present research. The analysis of the hearing health of the volunteers was performed considering the inter-patient results, the first exam being the reference for the second examination of the same patient. The exams were performed on the same day of the chemotherapy session, immediately prior to drug administration. At the first visit the anamnesis was collected, to identify otological histories or previous hearing complaints. External hearing meatus inspection was performed, and in the presence of foreign body or excess of cerumen, the patient was referred to the otorhinolaryngology sector and a return was scheduled after medical conduct.

The audiological evaluation was composed of acoustic immitance measurements (MIA) with tympanometry and acoustic reflex threshold of the contralateral afferent pathway; conventional tonal threshold audiometry (0.25 to 8 kHz); high frequency audiometry (10, 12 and 14 kHz); speech reception threshold (SRT); Speech Recognition Percentage Index (SRPI) transient stimulus evoked (TEOAE) and distortion product (DPOAE) otoacoustic emissions.

The result of the tympanometry guaranteed good condition of the middle ear for audiometry and emissions. The contralateral reflex evaluates efferent hearing functions. If the tympanometry indicated that it was impossible to perform the other tests, the patient was referred to the otorhinolaryngology sector and after medical conduct another audiological examination was scheduled. After acoustic immitance measurements (MIA), conventional threshold tonal audiometry and high frequency audiometry were performed in an acoustically treated cabin. The audiometry of the Otometrics model Itera II was used to determine the hearing thresholds, with ANSI Standard calibration, using supra aural TDH 39 headphones for conventional tonal audiometry (0.25 to 8 kHz) and circumaural headphones for the calibration of the high frequency thresholds (10, 12 and 14 kHz). When the threshold exceeded 25 dB, the bone pathway was performed between the 0.50 and 4 kHz frequencies using a bone vibrator in the patient's mastoid region.

Otoacoustic emissions were performed with the Otodynamics ILO 92 clinical equipment, with the patient inside the sound box with a probe positioned in the external acoustic meatus. Good condition was guaranteed to perform the test, by observing probe stability, reproducibility and environmental noise. The transient stimulus evoked by otoacoustic emissions (TEOAE) were obtained in the 1, 2, 3 and 4 kHz frequency bands and the response amplitude should be 3 dB above the noise in at least three of these bands. Distortion product evoked by otoacoustic emissions (DPOAE) were performed between frequencies 1 to 8 kHz, with a frequency range of 1,000 Hz and were considered present when the response was 6 dB above noise.

The audiological examinations were performed in the two audiological appointments, on the same day of the chemotherapy session and immediately before the drug's administration. Subjects in this sample had chemotherapy protocol cycles with interval ranging from one to two weeks at medical criteria, and the audiological examinations were performed in concomitant cycles.

In the present research, a quantitative analysis of the data was performed, obtaining the means, standard deviations and statistical models for data interpretation. Audiometry and otoacoustic emissions (transient and distortion product) were interpreted using the two-way ANOVA, z-test for proportions and the Wilcoxon signal test. The significance level adopted in this analysis was 0.05 (5%), that is, values lower than 0.05 in the analyzes of each variable were considered statistically significant. For the analysis, the software Microsoft

Excel 2010 and GraphPad Prism 6 (2013) were used.

Results

The values of the mean hearing thresholds were separated by ear. No significant statistical difference was observed in hearing thresholds in the second examination compared to the first, but it was possible to observe the absence of 14 kHz frequency responses in the second examination in all patients and an increase in the mean of the other thresholds, mainly in the frequencies, as shown in the following tables.

The ANOVA test has not shown a statistically significant difference in the results obtained between the first and second TEOAE tests, although an increase in the responses was observed, especially in the higher frequencies. No statistically significant differences were found in the DPOAE in the results, however, it was possible to verify the absence of answers in the second examination in the left ear for the frequency of 8 kHz in contrast to an increase in the responses in the right ear for this same frequency. An increase in the responses of the higher frequencies can also be observed, although it did not present statistically significant value.

Table 1. High frequencies audiometry of the right ear in the two evaluations carried out

Volunteer	Comparison of the auditory thresholds of the high frequencies of the right ear between the first and second audiometry					
	10 kHz		12 kHz		14 kHz	
	1st exam (dBNA)	2nd exam (dBNA)	1st exam (dBNA)	2nd exam (dBNA)	1st exam (dBNA)	2nd exam (dBNA)
1	60	↓	75	↓	↓	↓
2	65	80	75	80	↓	↓
3	90	90	↓	↓	↓	↓
4	65	65	↓	↓	↓	↓
5	25	25	25	35	45	↓
6	85	80	70	80	70	↓

↓: absent answer

Table 2. High frequencies audiometry of the left ear in the two evaluations carried out

Volunteer	Comparison of the auditory thresholds of the high frequencies of the left ear between the first and second audiometry					
	10 kHz		12 kHz		14 kHz	
	1st exam (dBNA)	2nd exam (dBNA)	1st exam (dBNA)	2nd exam (dBNA)	1st exam (dBNA)	2nd exam (dBNA)
1	60	↓	80	↓	↓	↓
2	70	80	70	75	↓	↓
3	↓	↓	↓	↓	↓	↓
4	60	60	↓	↓	↓	↓
5	25	30	25	60	45	↓
6	70	70	70	70	70	↓

↓: absent answer

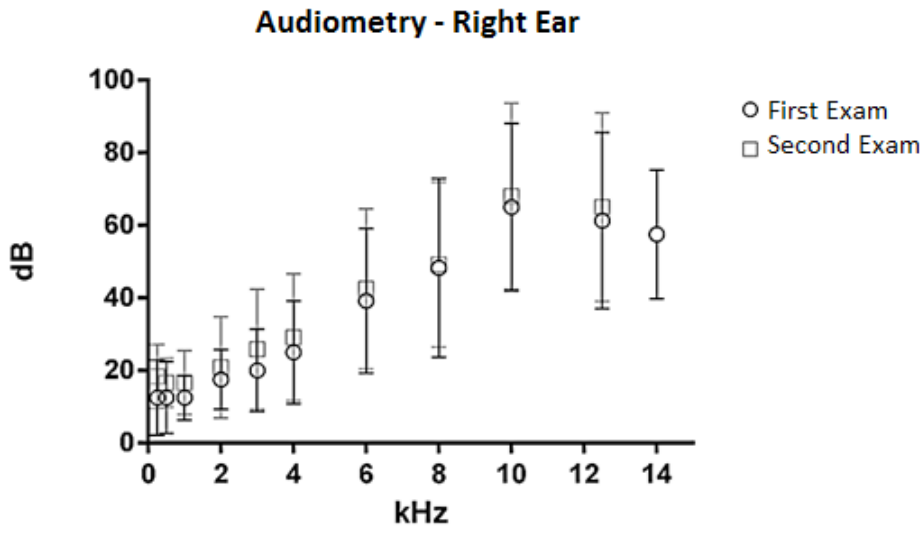

Figure 1. Average hearing thresholds of the right ear in conventional and high frequency audiometry

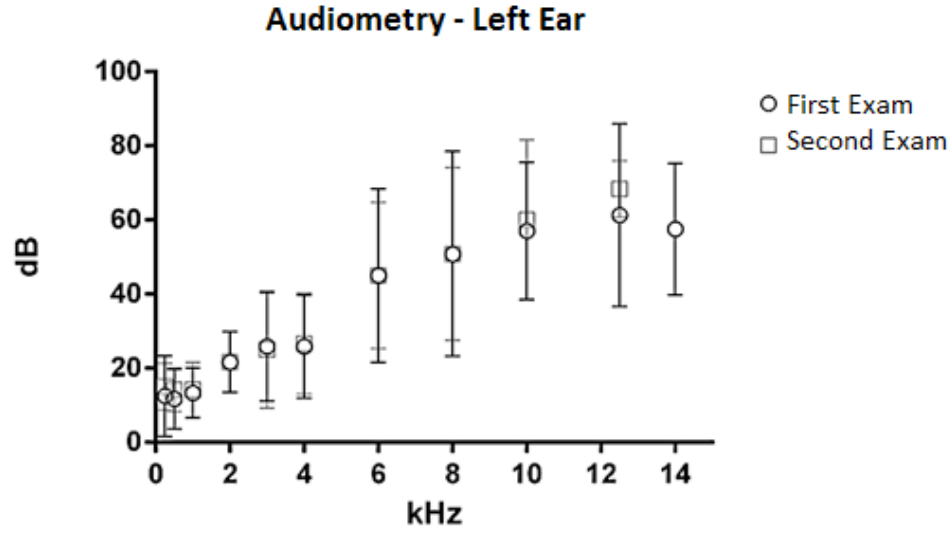

Figure 2. Average hearing thresholds of the left ear in conventional and high frequency audiometry

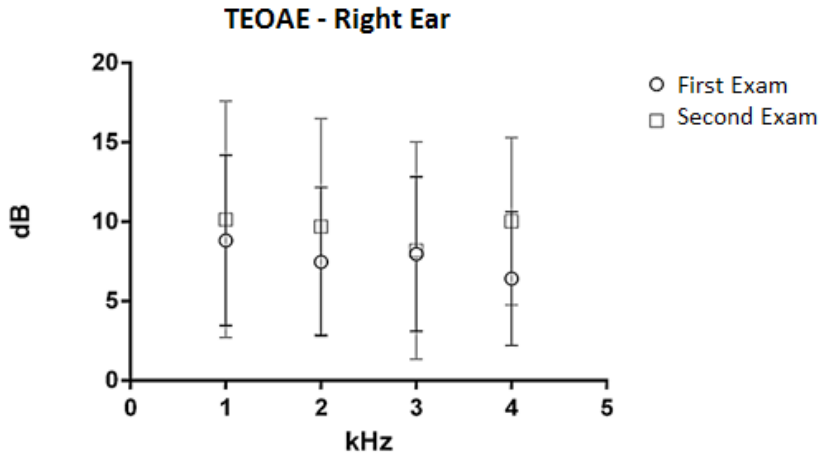

Figure 3. Comparison of the toae average amplitude of the right ear in the first and second examination

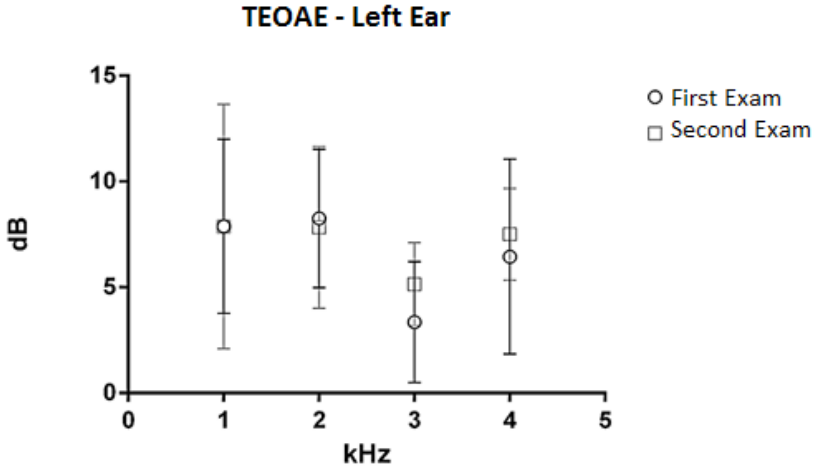

Figure 4. Comparison of the toae average amplitude of the left ear in the first and second examination

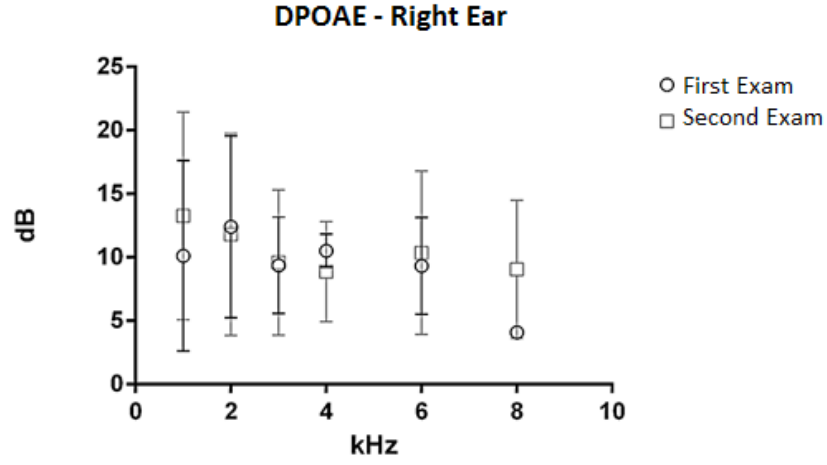

Figure 5. Comparison of the dpoae average amplitude of the right ear in the first and second examination

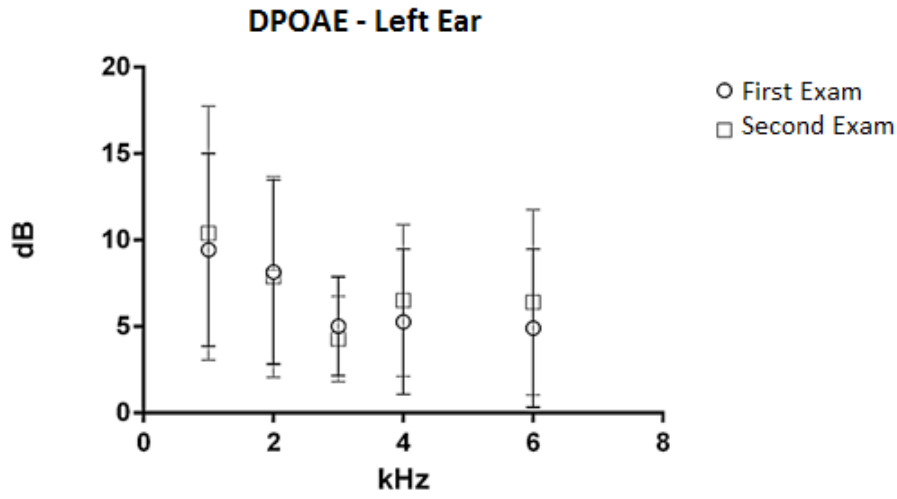

Figure 6. Comparison of the dpoae average amplitude of the left ear in the first and second examination

Discussion

The main goal of the chemotherapy treatment is the individual's organic cure; however, questions related to the quality of life after the cure should be debated and considered, since the survival of cancer patients has been increasing with the pharmaceutical and medical techniques. The use of ototoxic chemotherapeutics may cause irreversible hearing losses, of the sensorineural type and generally symmetrical, reflecting the quality of life of the individual. The reevaluation of the chemotherapy protocol, dose administration, otoprotect efficiency [21] or auditory rehabilitation can be considered in the scientific environment, to produce new clinical perspectives for the direct care of cancer patients.

Hearing monitoring for the adult oncology population is still sparse and not much performed, as evidenced by the small number of studies found in the literature regarding hearing monitoring in adults and in the average number of people aware of participation in the research. This may be due to questions related to the limitation in the perception of the importance of hearing monitoring by the medical team that take care of the patient, whose main goal is the organic healing of them; fragility and fatigue, both emotional and physical, concerning to the patient, restricting the availability of schedules of monitoring appointments, which require a certain periodicity; limitations of locomotion when the oncology and audiology services are not available in the same physical space.

Statistics on adherence to the treatment of chronic patients, oncological or not, have shown that educational measures are still necessary for the uptake and adherence of these patients, who often do not adhere to treatment as indicated by such issues as: disease severity, health, bureaucracies in access to the service, psychological difficulties in dealing with the disease, lack of knowledge about the disease and treatment, among other reasons [20, 22, 23, 24, 25]. The difficulty in patients' obtainance and adhesion in the present study was a limitation of this research regarding the number of the sample, as well as the obtaining of the audiological exams during the entire chemotherapy treatment, being the exams obtained only in two moments of the chemotherapeutic treatment. This fact shows the need to raise the awareness of physicians and the health team that take care of oncological patients about the importance of hearing monitoring as part of cancer treatment. As indicated in literature [15, 19, 26], the use of ototoxic drugs may cause alterations in auditory thresholds, especially of the higher frequencies, as observed in the mean auditory thresholds of the subjects of this research (GRAPHS 1 e 2), although it was not possible to observe significant changes in the present study, which presented the proposal of two audiological evaluations during the chemotherapy protocol, what was not able to monitor the hearing of the volunteers until the end and after the

chemotherapy. These data suggest the need for an extended auditory monitoring during and after the end of the chemotherapy treatment [17, 18, 19], in order to monitor the possible progression of changes in auditory thresholds and rehabilitate hearing if there is a significant auditory change that may impact the quality of life of the individual.

The present research found an increase in the signal-to-noise ratio of transient and evoked by otoacoustic emissions by distortion product (GRAPHS 3-6), in agreement to what was found by other authors [15], who studied a child-juvenile population in treatment with cisplatin, who reported increase otoacoustic emissions followed by their decrease.

This amplitude of otoacoustic emissions (OAE) increasing responses in subjects treated with cisplatin, which precedes the absence of responses, is related to a biochemical reaction of calcium and magnesium in the outer hair cells (ECC), which can lead to an alteration in ciliary mobility indicative of cell lesion and subsequent celular death, with consequent absence of responses in OAE [27]. There is no evidence in the literature relating carboplatin to these chemical reactions; however, the hypothesis that these reactions may occur with the use of carboplatin may explain the increase in OAE responses found in our study, and a follow-up of patients with periodicity can record if there is a decrease in OAE responses with increasing cumulative dose of the drug. Hearing monitoring studies in adults receiving chemotherapy with ototoxic drugs should awaken in the scientific community the need to study this population in order to provide the patient, through evidence-based conducts, the prevention of hearing losses due to chemotherapy and consequently the improvement of the quality of life after the organic cure.

Conclusion

From the comparative analysis of conventional and high frequency tonal thresholds in adults submitted to chemotherapy with carboplatin, no statistically significant values were found, and the same occurred in relation to the amplitude of otoacoustic emissions. However, hearing thresholds were worsened, especially at high frequencies, as well as increased amplitude of otoacoustic emissions, possibly related to subsequent cellular apoptosis.

Thanks

To the volunteers in this research and to Fundação de Amparo à Pesquisa Científica do Estado de São Paulo – FAPESP, which sponsored this research, subscribed by the number 2014/17737-9.

References

1. Oliveira JAA, Canedo DM, Rossato M. Otoproteção das células ciliadas auditivas contra a ototoxicidade da amicacina. Rev Bras Otorrinolaringol 2002; 68(1):7-13.

2. May BJ, Guarnieri M, Carson BS, Bachani A, Jallo GI. Long-term effects of carboplatin brainstem infusions on hearing thresholds in monkeys. Arch Otolaryngol Head Neck Surg 2004; 130:1411-5.

3. Hyppolito MA, Oliveira JAA. Ototoxicidade, otoproteção e autodefesa das células ciliadas da cóclea. Medicina, Ribeirão Preto 2005; 38(3/4):279-89.

4. Ltda., Laboratórios Pfizer. Bula Carboplatina. Pfizer. [Online] Laboratórios Pfizer Ltda. , 14 de Maio de 2014. [acessado em 19 dez 2016.] Disponpivel em: http://www.pfizer.com.br/sites/g/files/g10028971/f/product_attachments/PlatamineCS_PP_0.pdf

5. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989; 7(11):1748-56.

6. Gatzemeier U, Heckmayr M, Hossfeld DK, Zschaber R, Achterrath W, Lenaz L. Phase II study of carboplatin in untreated, inoperable non-small-cell lung câncer [abstract]. Cancer Chemother Pharmacol 1990; 26(5):369-72.

7. Almeida VL, Leitão A, Reina LCB, Montanari CA, Donnici CL. Câncer e agentes antineoplásicos ciclo-celular específicos e ciclo-celular não específicos que interagem com o DNA: uma introdução. Quim Nova 2005; 28(1):118-29.

8. Todd RC, Lippard SJ. Inhibition of transcription by platinum antitumor compounds. Metallomics 2009; 1(4):280-91.

9. Thomas JP, Lautermann J, Liedert B, Seiler F, Thomale J. High accumulation of platinum-dna adducts in strial marginal cells of the cochlea is an early event in cisplatin but not carboplatin ototoxicity. Mol Pharmacol 2006;70(1):23-9

10. Taudy M, Syka J, Popelář J, Úlehlová L. Carboplatin and Cisplatin Ototoxicity in Guinea Pigs: Les effets ototoxiques du cisplatine et du carboplatine chez le cobaye. Audiology 1992; 31:293-9

11. Lobarinas E, Salvi R, Ding D. Insensitivity of the audiogram to carboplatin induced inner hair cell loss in chinchillas. Hear Res 2013; 302:113-20.

12. Dalian D, Haiyan J, Yong F, Salvi R, Someya S, Tanokura M. Ototoxic effects of carboplatin in organotypic cultures in chinchillas and rats. J Otol 2012; 7(2):92-101.

13. Husain K, Whitworth C, Hazelrigg S, Rybak L. Carboplatin-induced oxidative injury in rat inferior colliculus. Int J Toxicol 2003; 22(5):335-42.

14. American Speech-Language-Hearing Association. Audiologic management of individuals receiving cochleotoxic drug therapy [Guidelines] 1994. [acesso em 19 dez 2016]. Disponível em: http://www.asha.org/policy/GL1994-00003/

15. Garcia AP, Iório MCM, Petrilli AS. Monitoramento da audição de pacientes expostos à cisplatina. Rev Bras Otorrinolaringol 2003; 69(2):215-21.

16. Knight KR, Kraemer DF, Winter C, Neuwelt EA. Early changes in auditory function as a result of platinum chemotherapy: use of extended high-frequency audiometry and evoked distortion product otoacoustic emissions. J Clin Oncol 2007; 25(10):1190-5.

17. Almeida EOC, Umeoka WG, Viera RC, Moraes IF. Estudo audiometrico de alta fraquência em pacientes curados de câncer tratados com cisplatina. Rev Bras Otorrinolaringol 2008; 74(3):382-90.

18. Peleva E, Emami N, Alzahrani M, Bezdjian A, Gurberg J, Carret AS, et al. Incidence of platinum-induced ototoxicity in pediatric patients in Quebec. Pediatr Blood Cancer 2014; 61(11):2012-7.

19. Yasui N, Adachi N, Kato M, Koh K, Asanuma S, Sakata H, et al. Cisplatin-induced hearing loss: the need for a long-term evaluating system. J Pediatr Hematol Oncol 2014; 36(4):241-5.

20. Costa JC, Buss CH. Análise de prontuários de pacientes oncológicos quanto ao monitoramento auditivo. Revista CEFAC 2009; 11(2):323-30.

21. van As JW, van den Berg H, van Dalen EC. Medical interventions for the prevention of platinum-induced hearing loss in children with cancer [abstract]. Cochrane Database Syst Rev. 2014; 1(7).

22. Reiners AAO, Azevedo RCS, Vieira MA, Arruda ALG. Produção bibliográfica sobre adesão/não-adesão de pessoas ao tratamento de saúde. Cien Saude Colet 2008; 13(2):2299-2306.

23. Kurita GP, Pimenta CAM. Adesão ao tratamento da dor crônica: Estudo de variáveis demográficas, terapêuticas e psicossociais. Arq Neuropsiquiatr 2003; 61(2):416-25.

24. Dewulf NLS, Monteiro RA, Passos ADC, Vieira EM, Troncon LEA. Adesão ao tratamento medicamentoso em pacientes com doenças gastrintestinais crônicas acompanhados no ambulatório de um hospital universitario. Revista brasileira de ciências farmacêuticas : RBCF 2006; 42(4):575-84.

25. Marques PAC. Pacientes com câncer em tratamento ambulatorial em um hospital privado: atitudes frente à terapia com antineoplásicos orais e lócus de controle de saúde. São Paulo. Dissertação [Mestrado em Enfermagem na Saúde do Adulto] – Universidade de São Paulo. 2006.

26. Landier W, Knight K, Wong FL, Lee J, Thomas O, Kim H, et al. Ototoxicity in children with high-risk neuroblastoma: prevalence, risk factors, and concordance of grading scales--a report from the Children's Oncology Group. J Clin Oncol. 2014 20;32(6):527-34.

27. Cevette MJ, Drew D, Webb TM, Marion MS. Cisplatin ototoxicity, increased DPOAE amplitudes, and magnesium deficiency. Distortion product otoacoustic emissions. J Am Acad Audiol. 2000;11(6):323-9.