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Evaluation of Ototoxicity in Patients Treated with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with Cisplatin

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Abstract

Objectives—Ototoxic hearing loss associated with intravenous or intra-arterial administration of cisplatin is well documented. However, there is limited data regarding the ototoxic effect of cisplatin when perfused into the abdominal cavity using hyperthermic intraperitoneal chemotherapy (HIPEC). The purpose of this study is to assess and describe ototoxicity in patients treated with HIPEC with cisplatin for peritoneal surface malignancies.

Design—We performed a retrospective chart review (2007–2012) of patients treated for advanced peritoneal malignancies at a tertiary care center using HIPEC with cisplatin and sodium thiosulfate infusion. Thirteen patients (12 males, 1 female) met study criteria. Audiometric thresholds were compared before and after treatment. A 20 dB loss at any single frequency, 10 dB decrease at any two adjacent frequencies, or loss of response at three consecutive test frequencies defined a significant ototoxic change (American Speech-Language-Hearing Association 1994).

Results—Despite minimal hearing change in 6 patients, none of the 13 patients in our study exhibited a significant ototoxic change in hearing sensitivity post HIPEC with cisplatin at any test interval in any test frequency.

Conclusion—Our findings represent the first objective assessment of ototoxic effect after HIPEC with cisplatin. Our results demonstrate that peritoneal perfusion of cisplatin with intravenous perfusion of sodium thiosulfate is not associated with ototoxic changes in hearing sensitivity. Further investigation of the systemic mechanism of absorption and potential ototoxic rescue effect associated with this chemotherapeutic regimen is needed to confirm these findings.

Keywords

cisplatin; HIPEC; ototoxicity; hearing loss; cancer

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INTRODUCTION

Ototoxicity is one of the dose-limiting side effects of cisplatin, a common chemotherapeutic agent that is widely used for oncologic treatment and has been strongly associated with hearing loss in adults and children. The incidence of ototoxicity associated with cisplatin-based chemotherapy varies as a function of patient age, dose, duration, and frequency of chemotherapeutic administration. The incidence of cisplatin-induced hearing loss has been reported between 11% and 91%, with an overall incidence of about 69% (Moroso & Blair 1983). Furthermore, hearing loss has been shown in 33% of patients who received doses of 60mg/m² of cisplatin, once every two weeks over a course of 7 weeks (Rademaker-Lakhai et al. 2006) with an incidence of over 50% in patients receiving cumulative doses greater than 400 mg/m² (Bokemeyer et al. 1998). In addition, ototoxicity has been reported in 33% of patients after a single dose of 50 mg/m² of cisplatin (Rademaker-Lakhai et al. 2006). Hearing loss, although typically characterized by a sensorineural hearing impairment in the high and ultra-high frequencies, may progress to lower frequencies over time. The hearing loss is typically bilateral, symmetrical, and permanent in nature. In addition, tinnitus may also occur as another ototoxic side effect (Hartmann & Lipp 2003). Thus, early detection of hearing loss in patients treated with cisplatin-based compounds may potentially allow for modifications in treatment dose, regimen, and schedule, to prevent ototoxicity in select patients.

In most cases, cisplatin is administered intravenously or intra-arterially as an adjuvant therapy, but may also be administered directly into the peritoneal cavity through hyperthermic peritoneal chemotherapy (HIPEC) (Gonzalez-Moreno et al. 2010). HIPEC is often preferred for pediatric and adult patients whose prognosis is poor because of advanced peritoneal disease consisting of hundreds of intra-abdominal tumor nodules (Hayes-Jordan et al. 2012). HIPEC is used in settings of multifocal abdominal disease that is often diffuse, primarily in patients with carcinoma (Sugarbaker & Jablonski 1995). HIPEC delivers heat in combination with chemotherapy into the abdominal cavity that provides cytotoxicity to residual microscopic cells that in turn has been shown to prolong life. The peritoneum affords a relative barrier allowing for higher doses of chemotherapy to be delivered into the abdominal cavity, without the systemic high dose associated toxicity, along with the added synergistic benefit from the heat. Cisplatin diffuses very slowly because it is a large molecule compared to the absorptive surfaces of the peritoneum so that less than 10% is absorbed into the blood stream (Dedrick et al. 1978; Howell et al. 1982; Dedrick 1985; Canal et al. 1989; Cho et al. 1999). HIPEC has most commonly been used to treat advanced stage ovarian, peritoneal, and gastrointestinal cancers, and in combination with doxorubicin, for abdominal soft tissue sarcomas. HIPEC is reported to control microscopic residual disease after surgical resection of abdominal tumors. Over the past 20 years, cytoreductive surgery in combination with HIPEC has been successfully used to treat some patients with extensive peritoneal neoplasms (Gonzalez-Moreno et al. 2010; Hayes-Jordan et al. 2012). In fact, our data has demonstrated an increase in overall 3-year median survival up to 71% for patients with desmoplastic small round cell tumor (a rare type of sarcoma), who receive cytoreductive surgery with HIPEC compared with 26% for patients who receive chemotherapy with or without radiation, and 62% for patients who receive surgery alone

(Hayes-Jordan et al. 2010). More recently, complete surgical resection with HIPEC in combination with adjuvant regimens of chemotherapy and radiation improved the median survival from 26.7 months to 63.1 months in this same group of patients (Hayes-Jordan et al. 2014).

HIPEC represents an aggressive technique with toxicities that include renal, hematologic, hepatic, and cardiac complications that can be severe, with reported grade III–V toxicity rates (Witkamp et al. 2001). Sodium thiosulfate is delivered intravenously as a rescue agent as part of the HIPEC procedure to mitigate chemotherapeutic toxicity (Hayes-Jordan et al. 2012). The intravenous delivery of sodium thiosulfate does not inactivate the effects of the intraperitoneal cisplatin because there is no bleeding during the HIPEC administration of the heated cisplatin.

Among the potential complications of HIPEC with cisplatin, ototoxicity has not been widely evaluated or clearly defined. Hearing is an important factor in the quality of life for patients facing end-of-life experiences, as well as for patients with the prospect for increased survival after treatment. Herein, we are the first to systematically evaluate the ototoxic effects of hyperthermic peritoneal perfusion of cisplatin using audiometric thresholds to determine significant ototoxic differences in hearing sensitivity.

MATERIALS AND METHODS

We conducted a retrospective data review and analysis of the audiometric thresholds of 13 patients, 7 who were treated on a prospective phase I/II trial (PI: AH-J) that was approved by the Institutional Review Board (IRB) at The University of Texas MD Anderson Cancer Center (UTMDACC) and 6 patients treated off-protocol, who received HIPEC with cisplatin and infusion of sodium thiosulfate for treatment of advanced peritoneal malignancies (2/2007–8/2012). Eligible participants were identified by a query of the UTMDACC Audiology Ototoxicity Monitoring Protocol Tracking Database. This study was approved by the UTMDACC IRB. A waiver of informed consent was obtained.

All patients were treated with HIPEC. A dose of 55–100 mg / m² of cisplatin was delivered through a continuous circuit, heated to 41 degrees Celsius for 90 minutes, in the operating room after complete surgical removal of the visible tumors. Sodium thiosulfate was delivered before, during, or after the HIPEC perfusion based on the patient's tumor response and toxicity to the chemotherapy and continued 12 hours postoperatively.

All patients received comprehensive baseline and post treatment audiometric testing and met the following inclusion criteria: (1) baseline hearing sensitivity within normal limits (0–20 dB HL) at all tested frequencies; (2) no pre-existing history of ototoxic treatment prior to HIPEC with cisplatin; (3) no history of other potentially ototoxic treatment during the ototoxic monitoring period; and (4) no active or recent history of middle ear disorders or abnormal tympanometric findings at the time of audiometric testing (baseline and post treatment).

Among the 46 patients who were reviewed, 13 patients (12 males, 1 female) met study criteria. The mean age at the time of HIPEC was 19 years (range: 10–30 years, median: 18

years). Cancer diagnoses included desmoplastic small round cell tumor (9), rhabdomyosarcoma (3), and liposarcoma (1).

Baseline audiometric thresholds were compared to thresholds obtained after HIPEC with cisplatin administration. Right and left ears were analyzed separately as audiometric threshold changes can be unilateral, bilateral, or asymmetrical.

Test Schedule

All patients received baseline audiometric testing prior to HIPEC administration (mean: 5 days, median: 3 days, range: 3–14 days) and were re-tested within 2 months following the procedure (mean: 32 days, median: 29 days, range: 11–55 days). Five patients returned for a second audiometric assessment within 3 to 4 months post HIPEC administration (mean: 4 months, median: 4 months, range 3–4 months). Four patients received a third follow up audiometric examination within 5 to 12 months post HIPEC (mean: 8 months, median: 7 months, range: 6–7 months). One patient underwent a second administration of HIPEC with cisplatin and subsequently received audiometric follow up testing 3 and 9 months after the second procedure, (8 and 15 months after the initial HIPEC).

Audiometric Assessment

Audiometric testing was completed in a sound-treated suite that met American National Standards Institute (ANSI 1969) specifications. Audiometric testing was conducted using Interacoustics Affinity audiometers. Sennhieser HAD A200 headphones were used for air conduction testing. Immittance testing was conducted using Interacoustics AT235h and Interacoustics Titan immittance bridges. All equipment met annual calibration standards. All testing was performed by a licensed audiologist (AW, RP, or JH). Audiometric thresholds were obtained binaurally for all subjects at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 k Hz. During the study period, the institutional ototoxicity monitoring protocol was expanded to include ultra-high frequency testing (above 8 k Hz to include 10, 12.5, 14, and 16 k Hz) to allow for earlier detection of ototoxicity compared with conventional frequencies alone (American-Speech-Language-Hearing-Association 1994). Therefore, 2 patients received testing only at conventional frequencies between .25-8 k Hz. Seven patients underwent conventional and ultra-high testing between .25-12.5 k Hz, and 4 underwent testing between .25-16 k Hz. Speech reception threshold (SRT) testing (SRT within 7 dB HL of the pure tone average of .5, 1, 2 k Hz, binaurally) was performed to verify the reliability of audiometric testing. Tympanometry was also performed to rule out middle ear involvement. Significant ototoxic changes were based on audiometric results only.

Criteria for Ototoxicity

A significant ototoxic change was defined as a decrease in hearing sensitivity that met any of the following criteria: (a) 20 dB HL decrease at any one test frequency, (b) 10 dB decrease at any two adjacent test frequencies, or (c) loss of response at three consecutive test frequencies where responses were previously obtained in a single ear (American-Speech-Language-Hearing-Association 1994).

RESULTS

At last follow up, 4 of the 13 patients were deceased (6–22 months post HIPEC) and 9 were currently living. Comparison with baseline audiometric thresholds following HIPEC with administration of cisplatin, revealed no significant change in hearing sensitivity at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 k Hz, binaurally, in any patient. All patients exhibited thresholds within a normative range of ± 5 dB compared to baseline thresholds, at each test frequency. Six patients exhibited a decrease in hearing sensitivity between 10–15 dB at a single tested frequency in one ear that did not meet the significant ototoxic criteria. None of the patients who received ultra-high frequency testing demonstrated any clinically significant change in hearing sensitivity in the conventional or the ultra-high frequency range. Furthermore, no clinically significant change in hearing sensitivity was found in any of the 5 patients who returned for additional follow up audiometric testing following HIPEC with administration of cisplatin or in the single patient who underwent HIPEC treatment twice. Figure 1 shows pre- and post- HIPEC audiograms for the study patients.

DISCUSSION

Our data represents the first objective analysis of ototoxicity in patients receiving cisplatin via a HIPEC procedure with abdominal perfusion of sodium thiosulfate. A 69% overall rate of ototoxicity has been reported when cisplatin has been administered intravenously or intra-arterially (Moroso & Blair 1983). In our study, 55–100 mg/m² of cisplatin was perfused directly into the peritoneal cavity with perfusion of sodium thiosulfate before, during, or after the HIPEC procedure. None of the patients we tested showed any significant change in hearing sensitivity compared with baseline thresholds. Although the timing of administration of the sodium thiosulfate (before, during, after) was important to nephrotoxicity, no ototoxic effect was demonstrated post HIPEC. Additionally, one patient received 2 courses of HIPEC with cisplatin and also failed to show any significant change in hearing sensitivity. This is an interesting and potentially significant finding as ototoxicity has previously been reported to occur in one-third of patients even after a single dose of 50 mg/m² of cisplatin administered intravenously (Bokemeyer et al. 1998). The use of sodium thiosulfate to mitigate chemotherapeutic toxicity is also interesting. Sodium thiosulfate has been used as a type of “chemotherapy rescue agent” to neutralize the systemic absorption of cisplatin into the body (Witkamp et al. 2001). Furthermore, cisplatin does not easily cross the peritoneal barrier, although there have been reported rates of systemic absorption up to 10% (Dedrick 1985; Hayes-Jordan et al. 2012). We postulate that our patients may not have experienced ototoxic effects because of these two factors: failure of the drug to be absorbed systemically and a rescue effect of sodium thiosulfate that may have mitigated potential chemotherapeutic circulation (Howell et al. 1982; Canal et al. 1989; Witkamp et al. 2001). Further investigation is needed to corroborate our findings and determine the exact etiologic mechanism that may prevent ototoxic hearing loss in patients receiving HIPEC with cisplatin and perfusion of sodium thiosulfate.

It is also possible that our inability to detect ototoxic change after HIPEC may have occurred because of a small sample size and limited long term follow up testing. Our study included 13 patients, 4 of whom succumbed to their disease 6 to 22 months (average: 11.7 months)

post-HIPEC, and several failed to return for follow up testing. It is possible that a longer follow up testing period may have detected an onset of hearing loss as late cisplatin-associated ototoxicity has been shown to occur after the cessation of treatment (Al-Khatib et al. 2010; Kolinsky et al. 2010). It will be important to establish an appropriate monitoring protocol in future studies to effectively detect potential ototoxicity in patients treated with HIPEC with cisplatin.

Our study evaluated ototoxicity following HIPEC with cisplatin in patients with peritoneal malignancies whose long-term survival is often limited. Recent reports, however, show increasing use of HIPEC as the treatment of choice for patients with advanced peritoneal disease with promising survival outcomes (Gonzalez-Moreno et al. 2010; Hayes-Jordan et al. 2010). Loss of hearing commonly causes social isolation and limits routine daily activities resulting in frustration and reduced quality of life. More important, hearing loss may prevent the ability to understand and contribute to important discussions involving critical decisions regarding medical management that often have life-influencing impact to the patient and family particularly at the end-of-life.

Despite the limitations of retrospective review and a small sample size, our findings are the first to systematically and objectively assess the ototoxic effect of peritoneal perfusion of cisplatin. Our results indicate that HIPEC with cisplatin and administration of sodium thiosulfate can be performed safely and is not associated with clinically significant ototoxic effect based on standard criteria for ototoxic change. HIPEC with cisplatin remains a viable therapeutic approach for adult and pediatric patients with peritoneal disease. Thus the findings from our study are also important as hearing preservation is critical to the quality of life for all patients but may be even more pressing for those with limited life expectancy.

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Figure 1.

Fig 1A and Figure 1B: Test results show no significant ototoxic change in hearing sensitivity, at any audiometric frequency, for either ear, for any of the subjects.