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Clinical Trial

COAST (Cisplatin ototoxicity attenuated by aspirin trial): A phase II double-blind, randomised controlled trial to establish if aspirin reduces cisplatin induced hearing-loss

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Abstract ***Background:*** Cisplatin is one of the most ototoxic chemotherapy drugs, resulting in a permanent and irreversible hearing loss in up to 50% of patients. Cisplatin and gentamicin are thought to damage hearing through a common mechanism, involving reactive oxygen species in the inner ear. Aspirin has been shown to minimise gentamicin-induced ototoxicity. We,

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therefore, tested the hypothesis that aspirin could also reduce ototoxicity from cisplatin-based chemotherapy.

Methods: A total of 94 patients receiving cisplatin-based chemotherapy for multiple cancer types were recruited into a phase II, double-blind, placebo-controlled trial and randomised in a ratio of 1:1 to receive aspirin 975 mg tid and omeprazole 20 mg od, or matched placebos from the day before, to 2 days after, their cisplatin dose(s), for each treatment cycle. Patients underwent pure tone audiometry before and at 7 and 90 days after their final cisplatin dose. The primary end-point was combined hearing loss (cHL), the summed hearing loss at 6 kHz and 8 kHz, in both ears.

Results: Although aspirin was well tolerated, it did not protect hearing in patients receiving cisplatin (p-value = 0.233, 20% one-sided level of significance). In the aspirin arm, patients demonstrated mean cHL of 49 dB (standard deviation [SD] 61.41) following cisplatin compared with placebo patients who demonstrated mean cHL of 36 dB (SD 50.85). Women had greater average hearing loss than men, and patients treated for head and neck malignancy experienced the greatest cHL.

Conclusions: Aspirin did not protect from cisplatin-related ototoxicity. Cisplatin and gentamicin may therefore have distinct ototoxic mechanisms, or cisplatin-induced ototoxicity may be refractory to the aspirin regimen used here.

1. Introduction

Cisplatin is a commonly used cytotoxic chemotherapeutic agent to treat a wide variety of cancer types, including head and neck, bladder, lung and germ-cell malignancies. In each of these diseases, cisplatin is used in curative as well as palliative treatment settings. Subsequently, adverse effects of treatment which are irreversible will potentially impact on patients for prolonged periods of time, thereby reducing health-related quality-of-life. Cisplatin has well-documented side-effects, including one of the highest rates of ototoxicity of all chemotherapy agents [1,2]. Cisplatin-related ototoxicity includes high-frequency bilateral and symmetrical hearing loss, which may be permanent and irreversible and is often associated with tinnitus [2,3]. Currently, there are no established methods to avoid or reverse cisplatin-related ototoxicity, other than dose reduction or switching to non-cisplatin regimens, which can have negative impacts on outcomes. Hence, ototoxicity risk must be weighed against oncological efficacy.

Fifty percent of patients receiving a cumulative cisplatin dose of >200 mg/m^2 have a significant reduction in their hearing, with a severe to profound hearing loss in both ears [2,4–6]: Using the American Speech–Language–Hearing Association criteria, this equates to >71 dB hearing loss, which clinically translates into the patient being aware of their hearing loss in most, if not all situations and only managing without a hearing aid if they concentrate and the speaker significantly raises their voice and if there are no competing sound sources [2].Clearly, this degree of hearing loss is very debilitating and may not always be appreciated by the clinician, on a one-to-one basis [7].

Ototoxicity from cisplatin is thought to be due, in part, to reactive oxygen species (ROS); ROS can be attenuated by antioxidants, such as salicylates, including aspirin. Gentamicin and cisplatin are thought to have a similar ototoxic mechanism of action. ROS lead to S-Nitrosylation of cochlear proteins causing damage to the outer hair cells, supporting cells, marginal cells of the stria vascularis, spiral ligament and the spiral ganglion cells [8]. The outer hair cells in the basal turn of the cochlea are the most affected [9,10], resulting in an initial elevation of high-frequency audiometric thresholds, followed by a progressive loss into the lower frequencies with continued therapy [11].

Aspirin was shown to prevent gentamicin-induced hearing loss without compromising its anti-bacterial efficacy in both animal models and in the clinical setting [12,13]. Patients treated with 1 g tds aspirin for 14 days, in addition to gentamicin, as part of a randomised controlled trial (RCT), showed a significant reduction in hearing loss compared with patients receiving gentamicin alone [12]. The incidence of significant hearing loss reduced from 13% in the placebo arm to 3% in the aspirin arm (relative risk 0.26, 95% confidence interval [CI] 0.08–0.86).

Aspirin has also been shown to protect hearing from cisplatin-induced ototoxicity in rats, using a breast cancer model [14]. Protection of hearing was achieved without apparent loss of anti-tumour efficacy of cisplatin.

We, therefore, sought to test if aspirin could reduce cisplatin-related hearing loss in a phase II RCT for