



## 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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## KEYWORDS

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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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## Ototoxicity; Hearing

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.

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## 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<sup>2</sup> 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

patients treated with a variety of cisplatin-based systemic anti-cancer therapy regimens.

## 2. Patients and methods

We performed a phase II RCT in patients receiving cisplatin-based chemotherapy in eight United Kingdom cancer centres.

Patients were eligible if they were 18 years or older and deemed suitable for a chemotherapy regimen containing a cumulative cisplatin dose of  $\geq 200$  mg/m<sup>2</sup>, with a maximum of two consecutive days cisplatin dosing per cycle, either as a single agent or as a combination chemotherapy. Key exclusion criteria included were as follows: prior cisplatin treatment; diagnosis of nasopharyngeal or skull base carcinoma (other head and neck tumours allowed); treatment plan requiring cisplatin for more than two or on non-consecutive days of a treatment cycle; therapeutic aspirin  $>75$  mg/day; prior history of haemorrhagic stroke, inflammatory bowel disease or haematological clotting disorders; absolute contraindication to aspirin/proton-pump inhibitors; symptomatic hearing loss which the PI considered excluded the use of cisplatin; pregnant/breast-feeding patients. Women of childbearing potential were required to have a negative pregnancy test performed within 7 days before trial drug administration, and all patients were required to use adequate birth control.

Baseline hearing tests were recorded before receiving the first cisplatin dose and included pure tone audiometry (PTA) and otoacoustic emissions (OAEs). A new technique has enabled non-linear components of the OAE to be recorded [15], showing that both second- and third-order non-linear components (Volterra Kernels), vk21–vk23 and vk31–vk33, are much more sensitive to minor hearing system damage than conventionally recorded responses [16]. These were repeated for 7 days ( $\pm 3$  days) after completion of the last cisplatin dose and again at 90 days ( $\pm 7$  days) after treatment.

Patients received up to six cycles of cisplatin-based chemotherapy, according to tumour site, response and toxicity. Aspirin at a dose of 975 mg tid, or placebo were administered orally, for 4 days in patients receiving cisplatin on a single day each cycle and for 5 days in patients receiving fractionated cisplatin chemotherapy on two consecutive days of each cycle (commencing the day before the first cisplatin administration, in both cases, to protect the hair cells from the cisplatin until it is bound to the plasma proteins or cleared via the kidneys). Omeprazole 20 mg or matching placebo was taken orally, once daily on the same days as the aspirin/placebo (i.e. patients received either both drugs or both placebos).

Blinding to drug/placebo allocation was achieved by formulation of a 975-mg enteric-coated aspirin tablet with a matched placebo. Omeprazole was sourced from

the commercial market and over encapsulated using an opaque gelatin capsule. A matched placebo for the omeprazole tablet was also over encapsulated (NuPharm Laboratories Ltd, Flintshire, UK).

The primary outcome was change in hearing loss during treatment (measurements taken before and at 7 days and 3 months after completion of cisplatin treatment) using PTA test at frequencies of 6 kHz and 8 kHz in both ears. Secondary outcome measures included assessment of other PTA test frequencies including 0.25, 0.5, 1, 2, 3 and 4 kHz at baseline and at 7 days and 3 months post-cisplatin; clinician-assessed level of hearing loss measured by the Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03; OAE profile before and after treatment (at 7 days and 3 months post-cisplatin); safety profile assessment using CTCAE and with specific focus on gastrointestinal and renal toxicity; assessment of treatment and concomitant medication compliance and cisplatin dose intensity.

Trial conduct was in accordance with the principles outlined in the International Conference on Harmonisation Good Clinical Practice guidelines and in compliance with the protocol, the Data Protection Act and all other ethical and regulatory requirements, as appropriate. Written informed consent was obtained from all study participants. The trial was sponsored by University Hospital Southampton NHS Foundation Trust and coordinated by the Southampton Clinical Trials Unit. Funding was from Cancer Research UK (C39812/A13344). EudraCT reference number: 2012-001509-25.

## 3. Statistical methods

The primary outcome was combined hearing loss (cHL) in decibels, assessed as total post-treatment hearing after chemotherapy (the sum of PTA measurements at 6 kHz and 8 kHz in both ears at the first time point after their last cisplatin dose), adjusted for baseline total hearing. This was assessed in the intention-to-treat (ITT) cohort using an analysis of covariance (ANCOVA) model adjusted for treatment arm and the stratification factor cisplatin dose. In addition, a ‘per-protocol cohort’ analysis and ‘protected cisplatin cohort’ (each cisplatin cycle received was ‘protected’ by either aspirin or placebo) analyses were planned as secondary outcomes.

**Supplementary Document 1** provides full details of the sample size. A total of 88 patients (44 per arm) were required, allowing for 80% power with a one-sided significance level of 20%. Patients were randomised using a web-based system on a 1:1 allocation, using block randomisation stratified by cisplatin dose.

## 4. Results

A total of 439 patients were screened to allow 94 patients to be recruited to the trial (45 to aspirin and 49 to

placebo): a reflection of block randomisation. Patients were recruited between 14-March-2013 and 09-July-2015, and were followed up for 3 months. The trial ended when a sufficient number of patients with baseline and at least one post-chemo PTA test were available.

Reasons for screen failure are detailed in Fig. 1. Demographic characteristics (age, gender and ethnicity) and hearing at baseline were balanced between arms (Table 1). Planned and actual cisplatin dose administered were also balanced between arms; however, some

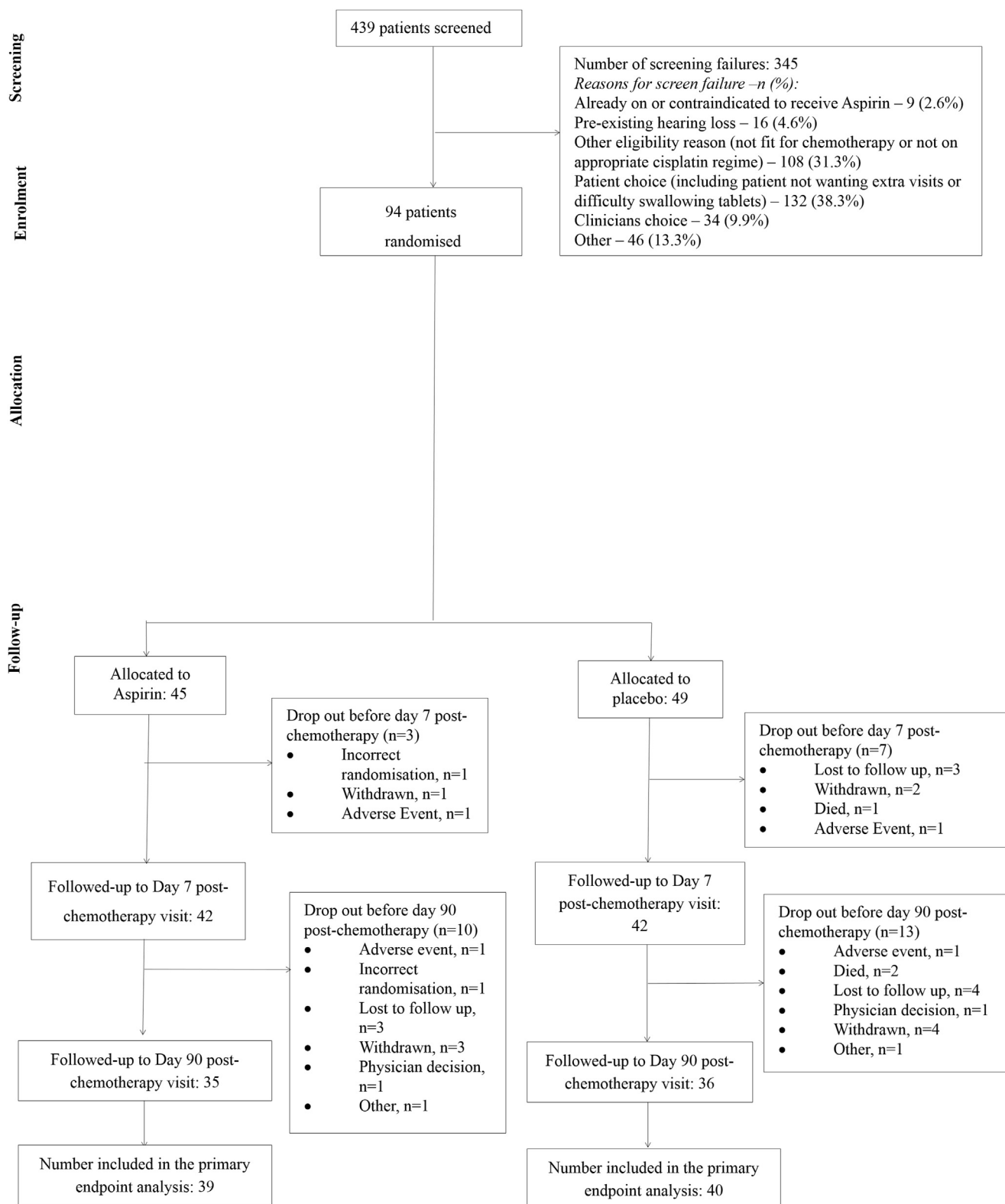


Fig. 1. CONSORT diagram for cisplatin ototoxicity attenuated by aspirin trial (intent-to-treat population, n = 94).

Table 1  
Patient demographics and tumour groups (intent-to-treat population, n = 94).

Characteristic	Aspirin (n = 45)	Placebo (n = 49)
Age at randomisation		
Mean (SD)	56.1 (11.20)	60.0 (11.78)
Range	24.0–75.0	27.0–79.0
Gender: n (%)		
Female	9 (20.0%)	13 (26.5%)
Male	36 (80.0%)	36 (73.5%)
Ethnicity: n (%)		
White	43 (95.6%)	48 (98.0%)
Asian or Asian British	0	1 (2.0%)
Black or black British	1 (2.2%)	0
Not stated	1 (2.2%)	0
Total baseline hearing <sup>a</sup>		
N	45	48
Mean (SD)	164.9 (70.93)	170.2 (85.88)
Range	–5.0 to 295.0	40.0–385.0
Planned cisplatin dose level: n (%)		
>200 mg/m <sup>2</sup> but <300 mg/m <sup>2</sup>	22 (48.9%)	24 (49.0%)
>300mg/m <sup>2</sup> but <400 mg/m <sup>2</sup>	11 (24.4%)	13 (26.5%)
>400 mg/m <sup>2</sup>	12 (26.7%)	12 (24.5%)
Actual cisplatin dose level: n (%)		
>200 mg/m <sup>2</sup> but <300 mg/m <sup>2</sup>	22 (48.9%)	22 (44.9%)
>300 mg/m <sup>2</sup> but <400mg/m <sup>2</sup>	12 (26.7%)	13 (26.5%)
>400 mg/m <sup>2</sup>	11 (24.4%)	14 (28.6%)
Tumour group: n (%)		
Bladder carcinoma	8 (17.8%)	15 (30.6%)
Germ cell	7 (15.6%)	5 (10.2%)
Head and neck	21 (46.7%)	14 (28.6%)
Lung	9 (20.0%)	15 (30.6%)
Number of patients who withdrew before treatment: n (%)	2 (4.4%)	1 (2.0%)
Number of patients who completed planned <sup>b</sup> treatment: n (%)	23 (51.1%)	25 (51.0%)

SD, standard deviation.

<sup>a</sup> Total baseline hearing is the sum of pure tone audiometry measurements at 6 kHz and 8 kHz in both ears before their first cisplatin dose.

<sup>b</sup> Planned treatment regimen (number of cisplatin cycles) as on baseline electronic Case Report Form (eCRF).

minor imbalances were seen with respect to tumour site (Table 1). There were trends of more bladder tumours in the placebo arm (15 versus 8) and more head and neck tumours in the aspirin arm (21 versus 14). Median inter-cycle time was the same between both arms (21 days) and there were similar doses of cisplatin received and cisplatin dose intensity between the arms (data not shown). Of note, gastrointestinal problems reported at baseline were greater in the placebo arm (22% versus 4%).

Patient follow-up is shown in Supplementary Table 1, detailing per-protocol and cisplatin-protected groups: 32 (71%) of the aspirin arm and 34 (69%) of the placebo arm attended both follow-up visits for PTA and OAE testing. Twenty-four patients also underwent OAE testing at baseline (aspirin: 9 and placebo: 15), which showed a bigger range of OAE in the placebo arm, but this was not significant (data not shown).

There was a difference between one or more days delay in chemotherapy administration between the arms 15 of 45 (33.3%) for the aspirin arm compared with 21 of 49 (42.9%) for placebo, resulting in 19 and 30 delayed cisplatin cycles, respectively. The individual reasons are outlined in Supplementary Table 2. Reasons for patients stopping treatment early are outlined in Supplementary Table 3 and show that these were similar between both arms.

Up to 75 mg per day of therapeutic aspirin was permitted for trial entry: Four patients (8%) of the placebo arm and six patients (13%) of the aspirin arm were taking up to 75 mg of aspirin at baseline: this had dropped to one patient for both arms at follow-up.

#### 4.1. Primary end-point

The primary end-point was cHL at 6 kHz and 8 kHz. In the ITT population, there was a mean cHL of 49.0 dB (n = 39; standard deviation [SD] 61.41) and 36.0 dB (n = 40; SD 50.85) in the aspirin and placebo arms, respectively. In the ANCOVA model, total post-treatment hearing was compared between the two arms after adjusting for total hearing at baseline and cisplatin dose level. There was no evidence to suggest that aspirin protects hearing (least squares mean difference = 9.38 [60% CI: –1.45 to 20.22; p-value = 0.233 at a 20% one-sided level of significance]; Table 2).

No evidence of statistically significant differences in total post-treatment hearing between aspirin and placebo arms was observed in the per-protocol or protected cisplatin populations (p-values = 0.300 and 0.344, respectively at a 20% one-sided level of significance; data not shown).

#### 4.2. Secondary end-points

At 90 days after completion of cisplatin chemotherapy, the cHL remained in the aspirin arm with a mean loss of 63.9 dB (n = 27; SD 52.59) and 37.3 dB (n = 30; SD 49.94) in the placebo arm. It can be seen (Fig. 2) that there was no substantial change in the cHL between days 7 and 90 (correlation coefficient equal to 0.95 [i.e. day 7 and day 90]). Hearing loss does not correlate with cisplatin dose ( $\geq 200$  mg/m<sup>2</sup> but <300 mg/m<sup>2</sup>,  $\geq 300$  mg/m<sup>2</sup> but <400 mg/m<sup>2</sup> or  $\geq 400$  mg/m<sup>2</sup>). Additional *ad hoc* analysis, dividing patients at baseline into normal and mild hearing and moderate or worse hearing showed that the better the initial hearing, the greater the subsequent hearing loss (Supplementary Fig. 1). However, there was no difference in ototoxic protection between these different hearing groups with aspirin or placebo (data not shown). In addition, age did not predict for hearing loss in these data although the sample size may preclude meaningful conclusion. In our data set, women lost more hearing than men (Supplementary Fig. 2) and patients receiving cisplatin for head and neck

Table 2

Analysis of covariance of combined hearing loss (first post-chemotherapy pure tone audiometry hearing test) (intent-to-treat population, n = 79).

Characteristic	Statistic			
Least squares means	Estimate	Difference	60% CI of LS mean	One-sided p-value <sup>a</sup>
Aspirin (n = 39)	218.80	9.38	(-1.45 to 20.22)	0.233
Placebo (n = 40)	209.40			
Model coefficients	Estimate	60% CI		Two-sided p-value
Aspirin arm	9.38	(-1.45 to 20.22)		0.466
Placebo arm	0 (Ref)	—		—
Intercept	61.22	(42.90–79.54)		0.006
Total hearing at baseline	0.85	(0.78–0.92)		<0.001
Dose level: ≥200 mg/m <sup>2</sup> but <300 mg/m <sup>2</sup>	7.48	(-5.58 to 20.54)		0.629
Dose level: ≥300 mg/m <sup>2</sup> but <400 mg/m <sup>2</sup>	-2.23	(-17.20 to 12.74)		0.900
Dose level: ≥400 mg/m <sup>2</sup>	0 (Ref)	—		—

CI, confidence interval; ANCOVA, analysis of covariance; LS, least squares; PTA, pure tone audiogram.

<sup>a</sup> Combined hearing loss assessed using ANCOVA model: Total post-treatment hearing post-chemotherapy (the sum of PTA measurements at 6 kHz and 8 kHz in both ears at the first time point after their last cisplatin dose) = intercept + treatment arm + total hearing at baseline (the sum of PTA measurements at 6 kHz and 8 kHz in both ears before their first cisplatin dose) + randomisation stratification factor dose of cisplatin.

cancer experienced the largest median hearing loss (Supplementary Fig. 3). OAE data confirm the PTA data (Supplementary Table 4).

4.3. Safety end-points

From the ITT population, 88.9% (40 of 45) of aspirin and 95.9% (47 of 49) of placebo patients experienced at least one adverse event (Supplementary Table 5). Renal toxicity affected more patients in the aspirin arm (17.8% versus 10.2%) although the majority of these were

CTCAE, version 4.03, grade I or II (Supplementary Table 6): By contrast, renal and serum biochemistry values did not appear to be altered by the administration of aspirin or placebo (Supplementary Table 7).

Interestingly, reported gastrointestinal toxicities were similar between arms; supporting the use of proton pump inhibitors to minimise any gastrointestinal toxicities. In addition, hearing toxicities were greater in the placebo arm (44.9% versus 28.9%; Table 3).

There were 20 of 22 (90.9%) and 22 of 24 (91.7%) aspirin and placebo arm patients, respectively,

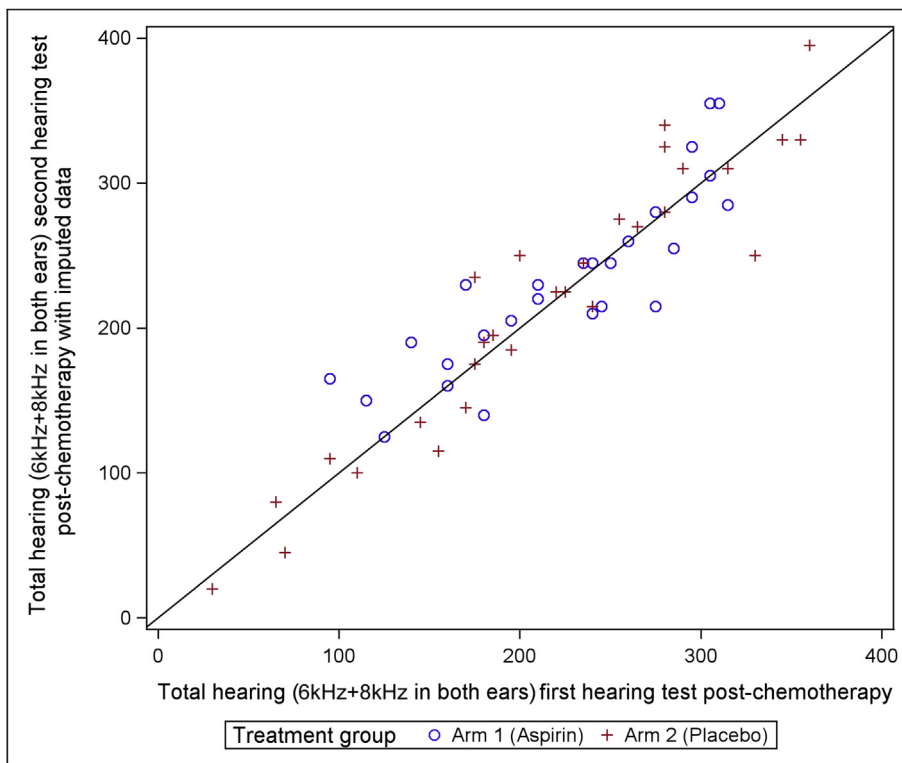


Fig. 2. Scatter plot to assess the relationship between the first and second pure tone audiometry hearing assessment values (intent-to-treat population provided two post-chemotherapy values, n = 57).

Table 3  
Hearing toxicity experienced during the trial period by CTCAE grade (intent-to-treat population, n = 94).

Characteristic	Aspirin (n = 45)	Placebo (n = 49)
Number of patients who experienced at least one hearing AE: n (%) <sup>a</sup>	13 (28.9%)	22 (44.9%)
Hearing adverse events: n (%) <sup>a</sup>		
CTCAE, version 4.03 grade I or II	13 (28.9%)	22 (44.9%)
CTCAE, version 4.03 grade III or above	0	0
Severe, life-threatening or death-related hearing adverse events (CTCAE, version 4.0 grade III or above): n (%) <sup>a</sup>	0	0
Inner ear toxicity	0	0

AE, adverse event; CTCAE, Common terminology criteria for adverse events.

<sup>a</sup> If a patient experienced more than one hearing AE with different CTCAE grades, then the worst CTCAE grade is counted in this table.

reported as having serious adverse events (SAEs), but only two patients were reported as experiencing serious adverse reactions (SARs).

## 5. Discussion

Aspirin was well tolerated but did not protect hearing in patients when combined with cisplatin chemotherapy. Aspirin was protective in a prior study of patients receiving gentamicin (although describing a different primary end-point), suggesting that either cisplatin and gentamicin have distinct ototoxic mechanisms (and aspirin would not have been protective at any dose) or cisplatin in the cumulative doses required for most cancer indications, is perhaps more ototoxic, requiring larger (and potentially impractical) or prolonged protective doses [12]. As an antimicrobial agent, gentamicin is expected to reach a relatively steady state in contrast with cisplatin, which relies on a maximally tolerated dose; which leads us to the possibility that perhaps an increased aspirin dose to compensate for this would have provided ototoxic protection. In addition, the question of aspirin-related ototoxicity should be raised although it is unlikely to result in any permanent or irreversible ototoxicity at the short duration administered in this trial [17]. With regard to duration of aspirin administration, we chose to evaluate a 4- or 5-day schedule starting 24 h prior, until 2 days after, cisplatin on each cycle. The rationale for this approach was to optimise aspirin exposure to the duration of peak cisplatin exposure. The clearance of total platinum from plasma is rapid during the first 4 hours after intravenous administration and decays monoexponentially with a half-life of about 20–30 minutes following bolus administrations of 50 or 100 mg/m<sup>2</sup> doses. However, there is then a prolonged low exposure to plasma protein-bound platinum that may persist for many years after cisplatin administration and might potentially account

for a failure to address acute ototoxicity through the approach tested here [18–20].

It is interesting that, despite the negative PTA and OAE (Supplementary Table 4) results, hearing toxicity, as perceived by patients, was significantly worse in the placebo arm (Table 3). At this time, PTA is the gold standard for quantifying hearing loss. However, we accept that it does not capture qualitative, patient-related outcome, and this may explain the reported differences.

Our data did not show any significant deterioration in the acute setting between day 7 and day 90 (Fig. 2). This contrasts with previously published data that have shown increased hearing loss after completion of cisplatin over a chronic time course over many months and years, which has been explained by the long-term (up to 20 years) retention of this compound [19,20]. It is feasible that continued follow-up of our patient cohort could have demonstrated this chronic continued deterioration that we did not identify in the acute setting.

Patients with better hearing at baseline were at greater relative risk of hearing loss following cisplatin (Supplementary Fig. 1). This is likely to reflect the number of functional hair cells that can potentially be destroyed by cisplatin in those patients with good hearing [14]. This may be important clinically as cisplatin might tend to be avoided, based on treatment guidelines, in patients with pre-existent poor hearing to minimise the risk of further deterioration. However, the greatest risk of harm, in absolute terms, may in fact reside with those patients with good hearing initially. This is perhaps counterintuitive to many clinicians in their approach to the use of cisplatin in routine practice, and guidelines should be considered for this patient group.

Women suffered greater hearing loss than men (Supplementary Fig. 2). Previous papers have published hearing loss data associated with cisplatin in discrete disease types (i.e. gynaecological and testicular cancers) where gender differences would not have been highlighted [21,22]. However, a rat model supports our gender difference by demonstrating adult female rat predisposition to increased cisplatin toxicity: this resulted in an increased audiometric loss and histopathological correlation, reflecting increased damage in the spiral ganglion and brainstem of female rats [23]. By contrast, in the paediatric population, boys are four times more likely to suffer from cisplatin-induced ototoxicity than girls, perhaps reflecting hormonal protection [24].

It is well established that an increasing dose of cisplatin is associated with an increasing risk of ototoxicity [11]. In contrast to this and to the data recently published [2], cisplatin dose in our cohort did not correlate with ototoxic potential. In the Frisina germ-cell cohort, greater or less than 300 mg/m<sup>2</sup> cisplatin stratified patients into severity of hearing loss [2]. It is likely that our smaller sample size, across multiple tumour types, contributed to this lack of effect.

We demonstrated that head and neck cancer patients experienced the largest median hearing loss (Supplementary Fig. 3): This may have resulted from the concomitant radiotherapy that this patient population would also have received, which despite cochlear sparing (Intensity Modulated Radiotherapy, IMRT) protocols, may still induce a degree of cochlear damage [25,26]. Although this is unlikely to have introduced significant bias into the trial, it is important to highlight that there were more head and neck patients in the aspirin arm and more bladder patients in the placebo arm. Despite being a younger cohort with better baseline hearing, germ-cell patients surprisingly did not show worse hearing loss (Supplementary Fig. 3).

## 6. Conclusion

Although aspirin was well tolerated, it did not protect hearing at the doses and in the schedule investigated here, suggesting that cisplatin and gentamicin may have distinct ototoxic mechanisms or that cisplatin is more ototoxic, requiring larger protective doses. Qualitative data did suggest a protective effect of aspirin, but this trial was not powered to test this hypothesis. Cisplatin-induced ototoxicity results in significant morbidity, and further research is required to devise options to prevent it.

## Conflict of interest statement

None declared.

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ISRCTN Registry Clinical Trial Registration Number: ISRCTN83689269.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejca.2017.09.033>.

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