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Original Research

Determinants of ototoxicity in 451 platinum-treated Dutch survivors of childhood cancer: A DCOG late-effects study

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Abstract Platinum-containing chemotherapeutics are efficacious for a variety of pediatric malignancies, nevertheless these drugs can induce ototoxicity. However, ototoxicity data on large cohorts of childhood cancer survivors (CCSs) who received platinum agents, but not cranial irradiation are scarce. Therefore, we have studied the frequency and determinants of ototoxicity in a cross-sectional multicenter CCS

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cohort, including the role of co-medication since it has been suggested that these play a role in ototoxicity.

We have collected treatment data and audiograms from the medical records of CCS treated in the seven pediatric oncology centres in The Netherlands. Ototoxicity was defined as Münster grade ≥2b (>20 dB at ≥4–8 kHz).

Four-hundred-fifty-one CCS who received platinum agents, but not cranial irradiation (median age at diagnosis: 4.9 years, range: 0.01–19 years) were included. The overall frequency of ototoxicity was 42%. Ototoxicity was observed in 45% of the cisplatin-treated CCS, in 17% of the carboplatin-treated CCS and in 75% of the CCS that had received both agents. Multivariate analysis showed that younger age at diagnosis (odds ratio [OR]: 0.6, 95% confidence interval [CI]: 0.5–0.6 per 5 years increase); higher total cumulative dose cisplatin (OR: 1.2, 95% CI: 1.2–1.5 per 100 mg/m^2 increase); and co-treatment with furosemide (OR: 2.3, 95% CI: 1.4–3.9) were associated with ototoxicity.

We conclude that treatment with (higher total cumulative dose of) cisplatin, young age and furosemide co-medication independently are associated with an increased risk of ototoxicity in CCS. Future prospective studies are necessary to confirm the additive risk of co-medication on the development of ototoxicity.

1. Introduction

Late-effects of cancer treatment have gained more attention because of the increasing number of survivors. A Dutch study showed that 75% of 1362; 5-year survivors of childhood cancer treated before 1996 had at least one low burden side-effect [1]. Problems with ear, nose and throat, including ototoxicity, were reported in 108 survivors of which 17% showed mild to severe problems. Ototoxicity is an important side-effect of platinum-based chemotherapy. This is characterised by irreversible, bilateral loss of high frequencies and is commonly accompanied by tinnitus [2]. This is relevant, as hearing impairment in children seriously influences speech, language and subsequent social-emotional development. Furthermore, it enhances the risk of learning difficulties [3–6].

Cisplatin and carboplatin are effective chemotherapy agents for a variety of pediatric malignancies, but they are also notorious for ototoxic side-effects. However, several previous studies showed a wide range in the frequency of reported ototoxicity (11%–73%) [2–5,7–14]. Most of these studies were small-scale [3,4,15] and focused on patients who got cranial radiotherapy [3,8,9,16]. Because cranial radiotherapy is a very strong determinant of ototoxicity, it is hard to examine the independent ototoxic effects of cisplatin and carboplatin. Therefore studies focused on patients that were not treated with cranial radiotherapy are needed. Children receiving chemotherapy are often given diuretics to attain diuresis or antimicrobial drugs to treat infections. It has been suggested from adult studies that this co-medication may increase the risk of ototoxicity. Vancomycin has been associated with ototoxicity in adults, mice and guinea pigs [17–20], but there have been no studies on this type of co-medication in childhood cancer survivors (CCSs). The lack of published results highlighting the risk of ototoxicity from non-chemotherapeutic ototoxic co-medication in platinum-treated pediatric patients, impedes the assessment of independently associated potential risk factors (Table 1) [8,10,12–14,21–25].

The aim of the present study was to determine the frequency and the determinants of ototoxicity (including the role of co-medication) in a large national multicenter cohort of survivors of childhood cancer who received platinum, but not cranial irradiation for the treatment of childhood cancer.

2. Patients and methods

Survivors of childhood cancer, <19 years at diagnosis, treated between 1980 and 2012 in The Netherlands participated if they met the following inclusion criteria: (1) received platinum agents; (2) not irradiated cranially or locally to ear/neck region; (3) available audiogram after stop treatment; (4) normal hearing before start of chemotherapy as assessed by medical records or hearing test. Data collection included demographics, cancer diagnosis, type and total cumulative dose (TCD) of platinum agent and use of assumed ototoxic co-medication (aminoglycosides, vancomycin and furosemide) as prescribed in the participating medical centres. This study was approved by the medical ethical committee (EMC:MEC-2015-269).

2.1. Audiometric evaluation

Pure-tone audiometry was performed at six different frequencies (0.25, 0.5, 1, 2, 4 and 8 kHz) in both ears to determine auditory sensitivity. Both bone and air