Ototoxicity and Chemotherapy: Genetics and Phenotypic Co-morbidity Analyses in Adult-Onset Cancer Survivors

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Platinum compounds are one of the most widely used groups of cytotoxic drugs worldwide. Each year more than 5.8 million patients are diagnosed with a cancer for which first-line therapy can potentially include platinating agents. Despite over 40 years of use, however, there are few means to identify patients at risk for cisplatin-induced ototoxicity or neuropathy who might be offered alternative therapy, improved symptom management, or reduced-dose regimens where possible. For patients who must receive cisplatin, there are no approved preventive measures and few therapies. To help fill these gaps, we established the first well-characterized clinical cohort of over 2,000 testicular cancer survivors (TCS) cured with homogeneous cisplatin-based chemotherapy, and studied the genetics of ototoxicity and neuropathy. Our baseline, cross-sectional results showed that 80% of TCS had hearing loss based on audiometric testing, with 1 in 5 classified as severe-to-profound; 56% had neuropathy; and 40% had tinnitus. We found that a SNP (rs62283056) in deafness gene *WFS1* was related to hearing loss ($P=1.4x10^{-8}$) and showed a significant interaction with cisplatin dose, thus having potential clinical impact to predict susceptibility. We also found a significant relationship between hypertension and hearing loss (P=0.007). In multivariate modeling, variables significantly related to neuropathy included age at TC diagnosis, smoking, excess drinking, and hypertension. Cisplatin-neuropathy was highly heritable, and common genetic variants explained up to 74% of phenotypic variability, suggesting a polygenic architecture. At a young median age (37 years), 38% TCS already had ≥3 adverse health outcomes (AHO). The cumulative burden of morbidity score (accounting for number, type and AHO severity) was high (≥2 grade 3 toxicities), very high (1 grade 4 toxicity), or severe (≥2 grade 3, and 1 grade 4 toxicity) in 20% TCS (median follow-up: 4.8 years). This is concerning since TCS are young at diagnosis, have an overall 97% 5-year survival rate, and could live upwards of 50+ years. Given this early burden, critical unanswered questions will be addressed in the future, where possible, with relations to hearing loss, speech perception and tinnitus: (1) characterization of the longitudinal trajectory of platinum toxicities, including the role of comorbidities and modifiable risk factors; (2) impact of toxicities on health-related quality of life and patient functioning; and (3) further elucidation of the role of genetic variation in platinum toxicities to identify high-risk subgroups. Comprehensive long-term follow-up will also permit identification of additional, later-emerging AHO, and the construction of validated risk-prediction models.

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