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

Lois B. Travis,* Paul Dinh, Matthew R. Trendowski, M. Eileen Dolan, Robert D. Frisina

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.

*Invited Presentation; #Submitting author’s information:
Lois B. Travis, M.D., Sc.D.
Lawrence H. Einhorn Professor of Cancer Research
Director, Cancer Survivorship Research Program
Indiana University Melvin and Bren Simon Cancer Center
535 Barnhill Drive RT433
Indianapolis, IN 46202
Email: LBTravis@IU.edu
Direct to Desk: #317-274-4875

Acknowledgment of Funding Sources
This work was supported by the National Institutes of Health “Genetic Susceptibility and Biomarkers of Platinum-related Toxicities” Grant (R01 CA157823) and the Pharmacogenomics Research Network (PGRN)-RIKEN Global Alliance (U19 GM061390)

Disclosure of Potential Conflicts of Interest:
The authors declare no potential conflicts of interest.