A Platinum Study Update

We thank you, the research study participant! The Platinum Study has now enrolled over 2,000 men throughout the U.S., Canada, and the U.K in this initial research phase. We continue to analyze data provided by you, and continue to present scientifically important information at national and international levels. One of our goals is to ensure that our findings are widely disseminated to clinicians and scientists. The sharing of scientifically important information is essential for providing the medical community with findings that may help you and future patients. This newsletter features one of our international collaborating researchers, Dr. Sophie Fossa, and includes summaries for two new publications that we hope will provide findings that may help you. To read more, please visit The Platinum Study website. As always, all data are presented in aggregate; no personal identifiers are used.

We sincerely thank you for your participation and encourage you to continue to consider participating in any future activities offered by this study. We will continue to carefully analyze the collected biologic samples and data to gain knowledge we believe will improve health outcomes for future patients.

Featured Clinician: Dr. Sophie Fossa

Our featured clinician in this issue is Sophie D. Fossa, M.D., Ph.D. Currently, she is Professor Emerita and Senior Researcher at Oslo University Hospital, Radium Hospital and the Cancer Registry of Norway. Dr. Fossa brings the perspective of an M.D. trained as both a medical and radiation oncologist and is an expert in multiple areas spanning the diagnosis, treatment, and follow-up of testicular cancer survivors. Dr. Fossa is world-renowned for her work, and has made groundbreaking contributions by founding the first cohort study of testicular cancer survivors in Norway. She has served as a close advisor to The Platinum Study since its inception in 2009. In Norway and in many international studies, Dr. Fossa has conducted research on all facets of survivorship (including post-treatment medical and psychosocial sequelae) for over 30 years, having treated many patients herself in Norway. Dr. Lois B. Travis, the lead investigator of The Platinum Study, notes, “Dr. Fossa is remarkable. She has a razor-sharp intellect, and has always been ahead of her time. She has a complete mastery of all facets of cancer survivorship and combines this with a genuine concern for patients and their families.” Dr. Fossa lectures nationally and internationally on survivorship topics and has co-authored hundreds of widely-cited research papers.
Background: When treating patients with testicular cancer, most doctors select a chemotherapeutic regimen that includes the drug cisplatin. Given its success, cisplatin-based chemotherapy is also used to treat many other cancers. While this combination chemotherapy regimen is very effective in curing testicular cancer, it comes with the risk of some degree of permanent hearing loss in both ears. This is called cisplatin-associated ototoxicity (ototoxicity means that something is toxic to the ear). About 18% (or 1 in 5) patients treated with cisplatin can experience profound hearing loss, particularly between 4 and 12 kHz, which is a range important for speech perception. This can be especially disturbing to patients who experience permanent hearing loss at a young age. Our research team wanted to understand if certain genes might make patients more at risk for developing cisplatin-associated ototoxicity.

What we did: The research team asked testicular cancer survivors enrolled in the Platinum Study if they would be willing to take a hearing test and provide a blood sample. Most of the survivors had received up to 300 or 400 mg/m² of cisplatin during their course of treatment. Blood samples were used to isolate the body’s genetic material, known as DNA. This DNA was then analyzed using a testing method called a genome-wide association study (GWAS), which searches for differences in genes between people who have a given disorder (in this case, hearing impairment) and people who do not have the disorder. Researchers can then identify genes that might make a person more likely to develop the selected disorder. In this case, the research team wanted to understand what genes might make a patient/survivor more likely to have cisplatin-associated ototoxicity.

What we found: After looking at millions of gene differences, the research team found that survivors who had a change, called a “mutation,” in the gene called WFS1 were more likely to also have cisplatin-associated ototoxicity. They also found that higher doses of cisplatin can make hearing loss worse in patients with this mutation. Interestingly, scientific researchers who study other types of diseases have shown that mutations in this gene can also cause deafness. Scientists believe that this mutation reduces the amount of an important protein (that is coded by this gene) that is available in inner ear sensory cells, which makes it harder for the cells to respond to agents which may cause damage (e.g., cisplatin). Thus, the Platinum Study research team suspects that having the WFS1 mutation and receiving cisplatin-containing chemotherapy makes it harder for cells to perform the way they should and makes patients more likely to experience hearing loss. The team underscored the importance of the replication of these findings, before any type of testing for mutations in the WFS1 gene is instituted. To a lesser degree, they also found that patients who developed deafness after cisplatin were more likely to have mutations in genes associated with other types of deafness. Thus, cisplatin-associated ototoxicity might occur in a way that is similar to other types of hearing impairment. It will be important to continue to do research in this area to better identify the mechanisms that cause cisplatin-associated ototoxicity, in order to eventually be able to either prevent this toxicity or lessen the effect of the cisplatin-associated damage.

The full published version of this article can be accessed from our website at:

http://cancer.iu.edu/platinum
Dr. Greg Steele knew the facts about testicular cancer before his diagnosis, but that did not make him immune. In fact, his oncologist, Dr. Larry Einhorn, asked Greg to explain the epidemiology of the disease to medical students while he was undergoing treatment. Twenty-five years later, Dr. Steele can still impress others with a wide knowledge of testicular cancer and its history, advancing from 95% death rate to 95% cure rate. He is not only a very knowledgeable epidemiologist, but also a participant in the Platinum Study.

Diagnosed in 1992, Greg Steele underwent chemotherapy before anti-nausea drugs worked well. He learned a lot from those in the room with him – a companionship develops in the hospital suite. Cancer patients understand each other in a way few others will comprehend. He believes in the work of The Platinum Study for two reasons. First, it helps him define his own symptoms and pass these along to his primary care provider to improve care. Second, he hopes the information he can provide will help improve and refine therapies for future individuals who receive a testicular cancer diagnosis.

Testicular cancer put things into perspective for Dr. Steele, spending time with people you care about being the most important. He loves his work as an epidemiologist at Indiana University and occasionally meets Dr. Einhorn by chance on campus. Thankfully, he no longer needs his phone number on speed dial. He is grateful he was at the right place at the right time if he had to get cancer and is happy that he can now give back to improve the lives of others through his experiences.
Clinical and Genome Wide Analysis of Cisplatin-Induced Peripheral Neuropathy in Survivors of Adult-Onset Cancer


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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect that some patients develop after they receive chemotherapy treatment. Men who received cisplatin-based chemotherapy to treat testicular cancer often experience CIPN as numbness, tingling, prickling feeling, loss of sensation, and pain in the areas of the body covered by gloves or stockings (e.g., finger, hands, toes, and feet). Doctors and scientists do not know why only certain people who receive chemotherapy develop CIPN or how to identify those who might be more at risk for developing CIPN. Further, there are currently no drugs to prevent or treat CIPN.

What we did: In this research study, the investigators asked men in The Platinum Study to: 1) answer questions about their health and cancer treatment, 2) have a physical examination, 3) allow the research team to use information from their medical records, and 4) allow researchers to obtain genetic information from a blood sample. Of the 680 participants, most were around 31 years (between 15 and 50 years old) at the time of chemotherapy treatment and around 38 at the time of participation in this study. It had been about five years since they had completed chemotherapy. Most patients received one of two drug combinations: 1) bleomycin, etoposide, and cisplatin or 2) etoposide and cisplatin.

The investigators used participant answers to questions; medical record information; and genetic data to understand why many participants experienced CIPN and what genes might be related to developing CIPN. More than half (56.2%) of the research participants reported problems with feeling or sensation in their limbs (hands/fingers and feet/toes), which are symptoms of CIPN. Participants who were older when diagnosed with cancer; who had a history of smoking; who had more than 2 drinks a day; or who had high blood pressure proved more likely to have symptoms of CIPN than other participants. Participants who had CIPN were more likely to say that they were in poor health and were more likely to have experienced weight gain. When investigators analyzed genes from the blood of participants, they found that participants with CIPN had reduced expression levels of two genes (MIDN and RPRD1B) and higher expression levels of one gene (THEM5). When investigators looked at the gene RPRD1B in other studies, they found that many individuals with decreased levels of RPRD1B also had peripheral neuropathy (CIPN).

What we found: There is still much work to be done, but this study showed that CIPN may be more likely to develop in chemotherapy-treated patients who are older or who have habits that are damaging to the body’s overall heath such as smoking or consuming larger amounts of alcohol. Additionally, there may be certain genes that make chemotherapy-treated patients more likely to suffer from CIPN, but these results still need to be confirmed in other studies. In the interim, these results stress the importance of a healthy lifestyle as part of a cancer survivor’s follow-up care plan.

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