IU study finds testicular cancer survivors may have hearing loss after cisplatin therapy

June 27, 2016

INDIANAPOLIS – Many testicular cancer survivors experience hearing loss after cisplatin-based chemotherapy, according to researchers at Indiana University.

The researchers, led by Lois B. Travis, M.D., Sc.D., the Lawrence H. Einhorn Professor of Cancer Research at the IU School of Medicine and a researcher at the Indiana University Melvin and Bren Simon Cancer Center, studied for the first time the cumulative effects of cisplatin-based chemotherapy on hearing levels in testicular cancer survivors through comprehensive audiometry measurements. They found that increasing doses of cisplatin were associated with increased hearing loss at most of the tested frequencies, involving 4, 6, 8, 10, and 12 kHz.

The research was published online June 27 in the Journal of Clinical Oncology.

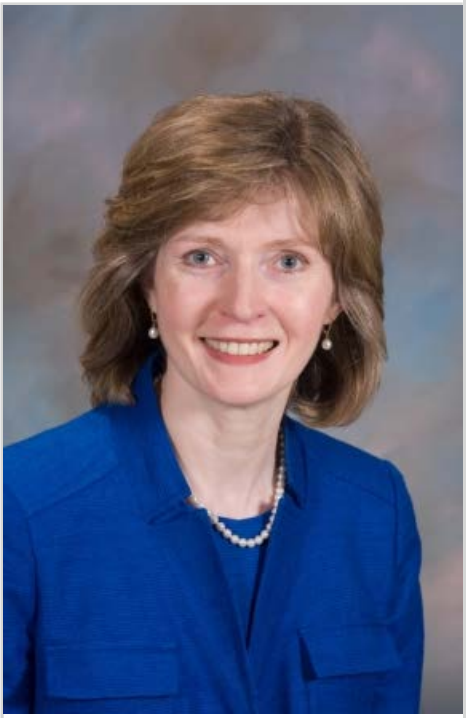
"In addition to hearing loss, about 40 percent of patients also experienced tinnitus (ringing-in-the-ears), which was significantly correlated with reduced hearing," Dr. Travis, also director of the cancer center's Survivorship Research Program, said.

Although this study was conducted in patients with testicular cancer, the authors point out that the general conclusions are likely applicable to patients with other types of adult-onset cancers that are commonly treated with cisplatin. They indicate that it will be important to follow patients given cisplatin-based chemotherapy long-term to better understand the extent to which the natural aging process may further add to hearing deficits, as it does in the general population.

"The results show the importance of comprehensive hearing assessments, preferably, both before and after treatments," Dr. Travis said. "Our findings suggest that health care providers should, at a minimum, annually query patients who have received cisplatin-based chemotherapy about their hearing status, consulting with audiologists as indicated. Patients should also be urged to avoid noise exposure, drugs having adverse effects on hearing, and other factors that may further damage hearing."

Co-first author Robert Frisina, Ph.D., added: "We are the first to show definitively that in a significant number of the cancer survivors, they have hearing loss above and beyond age-related hearing loss. They were of different ages --20s to 60s -- so this was a new analysis." Dr. Frisina is a professor in the Department of Chemical and Biomedical Engineering, director of the Biomedical Engineering Program, and director of the Global Center for Hearing and Speech Research at the University of South Florida. He designed the auditory portion of the study.

Platinum-based cisplatin is one of the most commonly used drugs in medical oncology that also has toxic effects on the inner ear. Despite its use for more than 40 years, knowledge about the effects of cumulative cisplatin dose on hearing loss in survivors of adult-onset cancer has remained limited.



Lois B. Travis, M.D., Sc.D.

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Lawrence H. Einhorn, M.D.

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The researchers found that every 100 mg/m^2 increase in cumulative dose of cisplatin resulted in a 3.2 dB impairment in hearing. The researchers also found high blood pressure was significantly related to hearing loss in these patients, even when cisplatin dose was taken into account. Thus, they emphasized the importance of high blood pressure control.

The researchers pointed out that because alterations in the highly successful testicular cancer regimens are unlikely for patients with advanced disease, their results underscore the importance of ongoing research aimed at the identification of genetic variants associated with cisplatin-related ototoxicity. An ultimate goal is to use the genetic results to develop effective agents that will protect the ear during the administration of cisplatin. For patients treated with cisplatin-based regimens for other types of cancer, it might also influence a physician to offer an alternative to those patients found to be genetically susceptible to the ototoxic effects of cisplatin after carefully weighing the risks and benefits of alternative treatments.

Lawrence Einhorn, M.D., Indiana University Distinguished Professor, Livestrong Foundation Professor of Oncology at the IU School of Medicine, and a physician scientist at the IU Simon Cancer Center, also was an author of the study.

In 1974, Dr. Einhorn tested cisplatin with two additional drugs that were effective in killing testis cancer cells. The combination became the cure for this once deadly disease. The results of this three-drug regimen were stunning. Tumors dissolved within days. Subsequent clinical research directed by Dr. Einhorn minimized the extremely toxic side effects of treatment; shortened the duration of two years of therapy to nine to 12 weeks; and established a model for a curable tumor, which has served as a research roadmap for generations of oncologists.

The researchers studied 488 men enrolled in the Platinum Study, which is open at the IU Simon Cancer Center and seven other cancer centers in the United States and Canada. The aim of the study is to gain new information that can benefit future testicular cancer patients and other patients treated with cisplatin-based chemotherapy.

The study was funded by a grant from the National Cancer Institute (R01CA157823).

Other authors included M. Eileen Dolan of the University of Chicago; Steven E. Lipshultz of Wayne State University School of Medicine; Shirin Ardeshir-Rouhani-Fard and Patrick Monahan of the IU Simon Cancer Center; Eileen M. Johnson and Sophie D. Fossa of Oslo University Hospital, Oslo, Norway; Amy Budnick and Darren R. Feldman of Memorial Sloan-Kettering Cancer Center; Clair J. Beard of Dana-Farber Cancer Institute; David J. Vaughn of the University of Pennsylvania; Robert Hamilton of Princess Margaret Cancer Centre; Howard D. Sesso of Brigham and Women's Hospital; Chunkit Fung and Sarah L. Kerns of J.P. Wilmot Cancer Institute; and Heather Wheeler of Loyola University.

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Scientists identify biomarkers that predict graft-versus-host disease after stem cell transplants

June 22, 2016

INDIANAPOLIS -- Researchers have identified biomarkers that could serve to predict which patients are more likely to be affected by chronic graft-versus-host disease following stem cell transplants. The identification of the four-biomarker panel could impact early detection and eventually treatment of the disease.

Chronic graft-versus-host disease remains the most common long-term complication of allogeneic hematopoietic cell transplantation -- the transplant of stem cells from one person to another. Allogeneic transplants are used to treat blood and bone marrow cancers such as leukemia and multiple myeloma, often as a last resort. Graft-versus-host disease occurs when immune cells from the transplant interpret the patient's body as foreign and attack it. Chronic graft-versus-host disease occurs in up to 70 percent of patients who survive 100 days past transplant, and is also the leading cause of non-relapse mortality.

The biomarkers were identified and validated by a national team of researchers comprising the Chronic Graft-Versus-Host Disease Consortium, including study co-lead author, Sophie Paczesny, M.D., Ph.D., professor of pediatrics and immunology at the IU School of Medicine. The study was published in the Journal of Clinical Oncology.

Chronic graft-versus-host disease can act like an autoimmune disease, affecting several organs of the body, inhibiting mobility, limiting quality of life, and can last throughout a patient's life.

"Currently, the only way to diagnose chronic graft-versus-host disease is a complex clinical evaluation of the patient for any symptoms of the disease after the transplant," said Dr. Paczesny. "With the discovery of a biomarker for the disease, a blood test can be created to replace this clinical evaluation, saving time and hopefully, providing more accuracy in predicting the occurrence of disease."

The researchers analyzed proteins in the blood plasma of patients with and without the disease to determine which proteins differed most significantly between the two groups. Protein analysis identified a four-biomarker panel that was significantly associated with subsequent development of chronic graft-versus-host disease. Researchers also analyzed proteins in patients three months before they showed clinical signs of the disease, discovering that these patients already showed elevated levels of the biomarkers.

"This means that even before the clinical signs of the disease were present, the biomarkers were elevated. This discovery provides us with even more information about the disease and suggests that we may be able to intervene earlier in patients with elevated biomarkers and prevent tissue damage," Dr. Paczesny said.

With the biomarkers providing some indication that a patient is likely to develop chronic graft-versus-host disease, researchers hope to be able to develop more targeted treatment options. Current treatment for the disease includes the administration of steroids, which must be tapered off slowly to avoid flare-ups of the

Sophie Paczesny, M.D., Ph.D.

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disease. The identification of the four proteins in the biomarker panel will assist scientists in developing more targeted therapies to treat chronic graft-versus-host disease.

“Much like chemotherapy is a global treatment for cancer, steroids are a general treatment for complications of chronic graft-versus-host disease, but they’re not specific,” Dr. Paczesny said. “These biomarkers will make it possible for us to discover more targeted treatments in the future.”

Other researchers contributing to the study included first author Jeffrey Yu, Kushi Kushekhar and Mohammad Abu Zaid of the IU School of Medicine; study co-lead author Stephanie J. Lee, Barry E. Storer, Paul J. Martin, Mary E. Flowers, John A. Hansen, Qing Zhang, Philip R. Gafken and Yuko Ogata of the Fred Hutchinson Cancer Research Center; Mukta Arora of the University of Minnesota; Corey Cutler of the Dana-Farber Cancer Institute; Madan Jagasia of Vanderbilt University; Joseph Pidala of the H. Lee Moffitt Cancer Center; Betty K. Hamilton of the Cleveland Clinic Foundation and George L. Chen of the Roswell Park Cancer Institute.

Dr. Paczesny is an investigator with the Herman B Wells Center for Pediatric Research and the Indiana University Melvin and Bren Simon Cancer Center.

The research was funded by grants (R01CA174667, R01CA118953, and U54CA163438) from the National Institutes of Health.

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5 questions with Dr. Lei Li

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***Lei Li**, PhD, is an associate professor of chemistry and chemical biology at the IUPUI School of Science. A member of the cancer center's Experimental and Developmental Therapeutics research program, Dr. Li has earned a $792,00 grant from the American Cancer Society.*

What can you tell us about your research? Also, what can you tell us about your research in which you received nearly $800,000 from the American Cancer Society?

Our research aims to reveal the roles of DNA lesions in cancer development, which fills an important gap in the current cancer research. DNA lesions lead to enhanced mutations and genome instability, which could ultimately result in cancer. Despite its importance, little effort is paid in biomedicine research to understand the chemistry and biology of DNA lesions due to the lack of effective analytical means. Our research adopts a multidisciplinary approach combining organic synthesis, mass spectrometry, enzymology, chemical immunology, and genomics to allow the understanding of a given DNA lesion in great detail.

Moreover, our approach may also enable us to analyze DNA lesions generated during radiation therapy. Connecting the lesions produced and the effectiveness of the therapy can potentially lead to personalized patient treatment and contribute to the development of precision medicine.

> "I am thrilled to see the IU-wide effort to integrate chemistry and medicine, as reflected by the recent Grand Challenges Program winning proposal on precision medicine."

The multidisciplinary approach enables us to demonstrate that a special thymine lesion named the spore photoproduct **,** which is currently considered to only exist in bacterial endospores, can actually form in human skin under solar radiation and is likely a major contributor to skin cancer. This finding represents a paradigm-shifting discovery in the DNA photobiology field. The American Cancer Society recognizes our groundbreaking work and funds our spore photoproduct skin studies via a four-year award. I am appreciative of the American Cancer Society's support.

How or why did you become interested in this particular area of research?

Trained as a synthetic chemist, I always dream to apply my chemistry expertise to “real” biomedical research improving human health. Being at a life science-oriented campus, I am offered numerous opportunities to interact with biomedical researchers, which allow me to shift my focus from mainly studying the chemistry side of DNA lesions to deeply understanding their roles in cancer induction. This area of research, in my opinion, is extremely important to our understanding of the molecular mechanism of cancer and our searching for effective therapy against cancer.

What’s the most rewarding part of your day?

Being able to utilize various chemical tools developed in my laboratory to tackle biomedical problems**,** which allow us to make unique contributions to biomedical research.

Outside of research, what are your other interests, hobbies?

Basketball, playing with my kids, wine, beer, gourmet food.

What attracts you to IU?

The collaborative environment and the close interactions with colleagues at the School of Medicine. Chemistry or chemical biology can play important roles in advancing medicine; however, the power of chemistry in biomedical research is drastically underexplored so far. I am thrilled to see the IU-wide effort to integrate chemistry and medicine, as reflected by the recent Grand Challenges Program winning proposal on precision medicine.

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News briefs

IU Simon Cancer Center hosts Cancer Moonshot Summit

In conjunction with the Cancer Moonshot Summit led by Vice President Joe Biden in Washington on June 29, nearly 20 researchers attended a campus summit hosted by the IU Simon Cancer Center.

Led by **Patrick Loehrer**, MD, director of the IU Simon Cancer Center, and **Bryan Schneider,** MD, the campus summit enabled attendees to gather to discuss IU's new Precision Health Initiative and how it might tie into the Cancer Moonshot.
The participants broke into small group discussions to develop provocative questions.

Vice President Biden called for a Cancer Moonshot Summit to take place on June 29, with a goal of having summits in communities across the country. The
summits were the first time that individuals and organizations representing the entire cancer community and beyond gathered under the national charge to double the rate of progress toward a cure.

Participants in the Cancer Moonshot Summit, hosted by the IU Simon Cancer Center, watch Vice President Biden deliver remarks from Washington.

The White House said more than 270 events were planned in all 50 states.

Cancer center member **Mark Geraci**, MD, represented Dr. Loehrer and the IU Simon Cancer Center at the summit in Washington.

"The Moonshot cannot be achieved by one person, one organization, one discipline, or even one collective approach, " Biden said in a statement. "Solving the complexities of cancer will require the formation of new alliances to defy the bounds of innovation and accelerate the prevention, diagnosis, treatment, and --ultimately -- a cure. It 's going to require millions of Americans speaking up and contributing what they're able. That 's what the Cancer Moonshot Summit is all about."

IU announces first round of funding for $300 million Grand Challenges Program

Indiana University has announced that the Precision Health Initiative, a research initiative focused on patient-centered precision medicine therapies, is the first recipient of funding under the university's new $300 million Grand Challenges Program.

Vera Bradley Classic raises more than $1 million

The recent Vera Bradley Classic, an annual golf and tennis event, raised more than $1 million for breast cancer research at the IU Simon Cancer Center. The Vera Bradley Foundation has raised more than $26 million of its $35 million pledge to the IU Simon Cancer Center, which houses the Vera Bradley Foundation for Breast Cancer Research Laboratories. Read Fort Wayne Journal Gazette editorial.

24 Hours of Booty raises more than $153,000

Earlier this month, more than 350 bicyclists took part in the annual 24 Hours of Booty to raise money for the IU Simon Cancer Center and Livestrong. Collectively, more than $153,000 was raised. The cancer center's team, Pedaling 4 Cures, raised $11,974. Thank you, booty riders!

New IUPUI camps map is available

Eager for a mobile-friendly way to get around IUPUI? IU Communications, University Information Technology Services and other partners have rolled out a digital campus map for the downtown Indy campus. IUPUI is the first IU campus to unveil its new digital version, but other campuses will soon be added to the list. Learn more.

ApeX Therapeutics files IND

ApeX Therapeutics, a biotechnology company focused on developing compounds to treat cancer, has filed an Investigation New Drug (IND) application with the FDA to evaluate the tolerability and anti-tumor effects of its lead drug candidate, APX3330. **Mark Kelley**, PhD, is the scientific founder of ApeX Therapeutics. Read news release.

Cancer center members in the news

- **Reuben Kapur**, PhD; **Rebecca Chan**, MD, PhD; **Yan Liu**, PhD; and others wrote "S6K1 Regulates Hematopoietic Stem Cell Self-renewal and Leukemia Maintenance," which was published in the Journal of Clinical Investigations. The authors wrote, "Given the recent interest in S6K1 as a potential therapeutic target in cancer, our results further support targeting this molecule as a potential strategy for treatment of myeloid malignancies."

- **Douglas Rex**, MD, has been named treasurer-elect to the American Society for Gastrointestinal Endoscopy's board of governors.

- **Mark Kelley**, PhD, and **Melissa Fishel**, PhD, have published the second edition of DNA Repair in Cancer Therapy. The authors provide a comprehensive overview of the basic and translational research into DNA repair as a cancer therapeutic target, including updates from the first edition. The book is available on store.elsevier.com.

- **Sunil Badve**, MBBS, MD, has been named to the Cancer MoonShot 2020's newly-formed Breast Cancer Working Group. The work group includes a team physicians, researchers, and oncology professors from across the nation who have come together to focus their collective wisdom and expertise to identify and develop the most effective cancer-directed immunotherapy treatments for breast cancer.

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- **Anirban Mitra**, PhD, earned the Schreiber Research Prize for Outstanding Mentored Investigators from the Ovarian Cancer Research Fund Alliance. The $5,000 prize is awarded to a junior researcher who can best demonstrate that he or she has been able to use prior OCRFA funding to impact the field of ovarian cancer research by making a significant discovery, making an important contribution to the literature, or transitioning to a full-time faculty position.

- June, designated Cancer Immunotherapy Month, is the perfect time to celebrate **Theodore Logan**, MD, the IU Simon Cancer Center's immunotherapy expert. The physician scientist has played a role in many of today's immunotherapies. Read feature story.

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