June 2010

IU researchers: Late-stage ovarian cancer shows promise in two-drug phase I trial

The combination of decitabine and carboplatin appears to improve the outcome of women who have late-stage ovarian cancer.

In the journal *Cancer*, IU researchers report four of 10 patients who participated in a phase I clinical trial had no disease progression after six months of treatment. One patient experienced complete resolution of tumor tissue for a period of time. Advanced ovarian cancer is often diagnosed too late for treatment to be effective. Patients are often told they have virtually no chance of recovery and only months to live.

Women participating in the study were between 51 and 71, and had previously exhausted all approved treatments for ovarian cancer. They enrolled in an IU Simon Cancer Center clinical trial designed to increase their sensitivity to the commonly prescribed ovarian cancer drug, platinum-based carboplatin.

Women with ovarian cancer usually survive less than one year after they become resistant to carboplatin and their cancer recurs, said co-principal investigator **Daniela Matei**, MD.


Matei

"Carboplatin is the most efficient drug therapy for ovarian cancer," Matei said. "Unfortunately, patients with recurrent disease become resistant to the drug after one or two rounds."

Decitabine was first used to treat the study patients intravenously daily for five days followed on the eighth day with carboplatin. After a month, the regimen begins again.

Six months after the trial began, four of the patients had no disease progression. At eight-and-a-half months, seven patients were alive (and at press time, still alive). Cancerous tissue in one of the patients shrank completely.

Adverse reactions to the treatment regiments were mild, including nausea, fatigue, and neutropenia (reduced white blood cell count).

Encouraged by the results of the phase I trial, which determined the safety of two different dosing regimens, a phase II trial is now under way with 17 patients already enrolled. Phase II trials are primarily focused on assessing the effectiveness of a drug or treatment protocol.

The study's other co-principal investigator, **Kenneth Nephew**, PhD, led the report's biochemical and DNA analysis.

In a bid to resensitize patients to carboplatin, Nephew and Matei and co-investigator **Jeanne Schilder**, MD, turned to the DNA demethylating agent, decitabine.

Why trial patients were responsive to the combination of decitabine and carboplatin is not yet known, but based on the literature and an analysis of biopsy tissue and blood samples, Nephew and Matei suspect decitabine reactivates tumor suppression genes that are turned off in ovarian cancer cells.

One of the hallmarks of ovarian cancer is the aberrant methylation of cytosine, one of DNA's four nitrogenous bases. Methylation prevents DNA readers from expressing genes. Some of the silenced genes won't be terribly important, but some, like tumor suppression genes, are. Decitabine is a known methylation inhibitor that can help return tumor suppression genes to an active state, and also improve cells' susceptibility to anti-cancer drugs like carboplatin.

"Our hypothesis is that decitabine isn't just targeting active ovarian cancer cells, but also cancer stem cells that seem to survive the first treatments," Nephew said. "By keeping tumor suppression genes from being methylated, carboplatin and other platinum-based treatments for ovarian cancer have a better chance of success in the late stages."

The researchers also reported that decitabine appears to have caused six of the 10 patients to become hypersensitive to carboplatin (a mild allergic reaction, treatable with steroids). While Nephew and Matei say that the effect may not be observed in a larger patient population, the scientists say they are intrigued by the phenomenon.

The two-drug treatment protocol is not approved for general use. The IU Simon Cancer Center is the only site for this clinical study.

June 2010

IU-OSU center gets $9 million more for cancer epigenetics

IU and the Ohio State University will receive $9 million from the National Cancer Institute to continue studying cancer genes and the sometimes-unnatural agents that mask the genes' expression, a phenomenon called epigenetics.

IU School of Medicine cancer biologist **Kenneth Nephew**, PhD, and OSU School of Medicine cancer geneticist Timothy Huang co-administer the OSU-IU Center for Cancer Systems Biology and its project, "Interrogating Epigenetic Changes in Cancer Genomes."

The project began in 2004 with about $8 million in NCI support. Ten other centers received funding or continued funding this year as part of the NCI's Integrative Cancer Biology Program.

"Our group uses integrated computational and experimental approaches to study epigenetic mechanisms that control signaling networks in prostate, breast, and ovarian cancers," Nephew said. "During the initial funding period, we focused on epigenetic processes associated with neoplastic transformation of normal cells into cancer cells. We demonstrated that disruption of key networks contribute to the development of breast, prostate, and ovarian cancer, and we developed mathematical models based on our experimental data."

Over the next five years, Nephew said the OSU/IU-led team will study epigenetic changes in prostate, breast, and ovarian cancer cells that cause resistance to hormonal therapy or traditional chemotherapy. Nephew said a major objective is to identify a panel of epigenetic biomarkers for predicting responsiveness to anti-hormone treatments and chemotherapies in cancer patients.

"These centers represent a unique multidisciplinary union of outstanding scientists and clinicians who will work to unravel the complexities of cancer through the novel application of technology and mathematical modeling," Dan Gallahan, NCI Integrative Cancer Biology Program director, said. "Their discoveries and models will be critical to our continued success in understanding and treating this disease."

The OSU-IU center also has an "Education Core," which is training young scientists to conduct integrated cancer research. During the initial funding period, the OSU-IU center

hosted 14 summer programs and co-organized two systems biology meetings. Center staff trained 137 undergraduate, graduate, and post-graduate students and supported the activities of more than a dozen short- and long-term visitors.

June 2010

Core spotlight

Transgenic and Knockout Mouse Core

The Transgenic and Knockout Mouse Core, established in 1990, provides timely and cost-efficient services in the production of transgenic mice and knockout mice for use in basic science research.

Loren Field, PhD, the core's director, explained the differences between transgenic mice and knockout mice. A transgenic mouse is one "that you add a piece of DNA that wasn't there formerly," while a knockout mouse is one in which scientists have modified a gene that was already present, he said.

Genetically engineered mice are regarded to be essential tools in understanding human diseases.

Located in R4, the core's services include:

- the production of transgenic mice (via pronuclear injection of recombinant DNA molecules)
- the production of knockout mice (via homologous recombination in ES cells)
- advice concerning construction of transgenic and gene targeting constructs, animal breeding, and maintenance of the resulting mouse colonies

For transgenic mouse production, investigators provide the DNA construct to the core. For knockout mouse production, the core provides three types of services: ES cell transfection, blastocysts injections, and rapid germ line breeding.

The core also offers embryo and sperm preservation and chimeric services.

For more information about the Transgenic and Knockout Mouse Core, contact William Carter at 278-0163.

News briefs

IUSCC, HOG sign memo of understanding

The IU Simon Cancer Center and Hoosier Oncology Group (HOG) have signed a formal memo of understanding, which clearly identifies HOG as the community clinical research arm of the IU Simon Cancer Center and the cancer center will serve as the research base for HOG. IUSCC researchers will propose new study ideas and follow through with submissions of grants and/or letters of intent to funding agencies to conduct studies in HOG. Meanwhile, HOG staff will provide support to IUSCC researchers throughout protocol development, writing letters of intent and support, and protocol writing. Overall, the memo of understanding creates clear obligations for each organization, ranging from financial support, community outreach, and pipeline fulfillment.

Volunteers needed to conduct free screenings during Allstate 400

Volunteers, led by **Michael Moore**, MD, from the IU Simon Cancer Center, the IU School of Medicine's Department of Otolaryngology - Head and Neck Surgery, and the Head and Neck Cancer Alliance will provide free oral, head, and neck cancer screenings during the Allstate 400 at the Brickyard July 24-25 at the Indianapolis Motor Speedway. If you would like to volunteer, contact Tamara Paal at tpaal@iupui.edu. Last year, the group screened more than 550 people and provided additional education and smoking cessation support.

NCI's caBIG annual meeting is Sept. 13-15

Join the National Cancer Institute for its 2010 caBIG® Annual Meeting - Building a Collaborative Biomedical Network - to:

- Learn about the critical importance of biomedical informatics and information technology in facilitating multidisciplinary collaboration across institutional barriers and advancing biomedical research
- Discover caBIG® capabilities that can support your work and share lessons learned with others who have developed and applied caBIG® technology to advance basic and clinical research
- Engage in unparalleled opportunities for networking and information exchange with leaders in biomedical informatics
- Investigate innovative tools and explore the caBIG® services-oriented architecture during hands-on sessions and demonstrations

The meeting is Sept. 13-15 in Washington, D.C. Visit the caBIG Web site for more details.

BioCrossroads seeks Life Sciences Champion of the Year; nominations due July 17

BioCrossroads is now seeking nominations for the Watanabe Life Sciences Champion of the Year, which will be awarded at the Indiana Life Sciences Summit on Wednesday, Oct. 27. To submit a candidate, go to http://www.biocrossroads.com/champion.aspx.

Criteria:

- Award is based on assessments of cumulative contribution, not on specific achievements over the course of a year
- Must be a resident of Indiana
- Must be an individual supporting Indiana's life sciences growth via corporate, academic, entrepreneurial, medical, philanthropic, or research work
- Must have made a significant achievement in the development and promotion of Indiana's life sciences industry
- Must personify the emerging face of the Indiana life sciences industry

Submission deadline is Friday, July 16.

Grants available to researchers

For the latest grant opportunities, visit the Funding Opportunities page on the IUSCC Web site.

Cancer center members in the news

- **George Sledge Jr.**, MD, a nationally recognized pioneer in the development of novel therapies for breast cancer, has started duties as president of the American Society of Clinical Oncology (ASCO), the world's leading professional organization representing physicians who treat people with cancer. He serves as president until June 2011.

- **Patrick Loehrer Sr.**, MD, was the recipient of the 2010 American Society of Clinical Oncology (ASCO) Special Recognition Award for his outstanding contributions to clinical oncology and cancer research and for his dedicated service to the oncology community. He was presented with the award during ASCO's annual meeting in early June in Chicago. In 2008, Dr. Loehrer was recognized with an ASCO Statesman Award for his service and commitment to the society.

- Four IU Simon Cancer Center researchers are among 62 top-ranking scientists and clinicians from seven countries selected to serve as inaugural members of the Susan G. Komen for the Cure's new Scientific Advisory Council. They are: **Sunil Badve**, MBBS, **Theresa Guise**, MD, **Kathy Miller**, MD, **Harikrishna Nakshatri**, PhD. The council will provide scientific peer review for the breast cancer grants and programs that Komen funds annually and will provide guidance on breast cancer education and public policy to Komen leadership. The council is focused on the organization's research program and the research with the best chance of providing effective treatments within 10 years.

- **Silvia Bigatti**, PhD, is one of two new Lilly Scholars. The Lilly Scholars awards support new faculty in public health recruited through national searches. The faculty expansion is being carried out to meet public health goals on the IUPUI campus. In addition to the honor that goes with the Lilly Scholar title, recipients receive start-up funds to help them develop research projects that will be submitted to the National Institutes of Health or other national peer-reviewed funding agencies. Dr. Bigatti is an associate professor in the Department of Public Health Division of Social and Behavioral Sciences. She joined the IU faculty in 2000 as an assistant professor of psychology. She holds a doctorate in clinical psychology with an emphasis in behavioral medicine from the University of California San Diego and the San Diego State University Joint Doctoral Program. She also completed a predoctoral internship at Yale University School of Medicine Department of Psychiatry. Dr. Bigatti's research will focus on factors related to stress and coping in cancer patients and their partners and also community-based preventive health behaviors among Latinos.

- **C. Max Schmidt**, MD, PhD, and colleagues reported in the May 2010 *Annals of Surgery*: "Cystic lesions of the pancreas are increasingly being recognized due to the widespread use of high resolution abdominal imaging. Since certain cyst types are precursors to invasive cancer, this situation presents an opportunity to intervene prior to malignant progression." The researchers explored whether glycosylation variants on specific proteins in cyst fluid samples could serve as biomarkers to aid in this diagnosis. They reported these results demonstrate the value of glycan variants for biomarker discovery and suggest that these biomarkers could greatly enhance the accuracy of differentiating pancreatic cystic tumors. Validation studies will be required to determine the clinical value of these markers, according to the researchers.

- **Mark Kelley**, PhD, and colleagues published "Novel Small Molecule Inhibitor of Ape1 Endonuclease Blocks Proliferation and Reduces Viability of Glioblastoma Cells" in the May 26, 2010, issue of *The Journal of Pharmacology*.

- In the May 2010 issue of *The American Journal of Pathology*, **Hari Nakshatri**, BVSc, PhD, **Sunil Badve**, MBBS, MD, FRCPath, and colleagues summarized that their "results suggest that subcellular localization of activated AKT plays a significant role in determining its function in breast cancer" in the article "Subcellular Localization of Activated AKT in Estrogen Receptor- and Progesterone Receptor-Expressing Breast Cancers."