January 2008

Research briefs

Renbarger studies vincristine

Jamie Renbarger, MD, has made two new discoveries with a drug that was approved in 1963, opening the door to new knowledge that may further help children with cancer. Renbarger knew that vincristine -- which is widely used to treat cancers in children – led to side effects that varied considerably between patients. But why? In the lab, she discovered that two enzymes, CYP3A5 and CYP3A4, metabolize vincristine differently. CYP3A5, which is found in approximately 70 percent of African-Americans and 10 percent to 20 percent of Caucasians, metabolizes vincristine much more efficiently than CYP3A4. Knowing which enzymes to target, Renbarger next compared toxicity in Caucasians with African Americans who had Acute Lymphoblastic Leukemia. She showed that Caucasians developed side effects – such as jaw pain, loss of reflexes, and constipation -- with vincristine more often than African-Americans possibly due to the fact that the CYP3A5 enzyme is found in fewer Caucasians. Currently, Renbarger is enrolling 140 children with preB acute lymphoblastic leukemia to determine the optimal dosing of vincristine for pediatric patients, which may improve survival for young cancer patients. Renbarger's studies tie into the Best Pharmaceuticals for Children Act (BPCA), which established a process for studying drugs used in children with the goal of improving pediatric therapeutics. Vincristine has been identified as a priority drug to study. Because of the ongoing studies at the IU Simon Cancer Center, Renbarger and her team are generating data unlike any other research currently underway.

Renbarger

Clapp, others make ground-breaking discoveries

In ground-breaking studies, Wade Clapp, MD, David Ingram, MD, and Fenchun Yang, MD, PhD, have discovered how to block certain signals that neurofibromatosis tumor cells use to "talk" to each other, leading to a series of on-going clinical trials that may reduce morbidity and mortality of children with neurofibromatosis, especially the plexiform variant. In particular, Clapp and his colleagues have discovered that imatinib (Gleevec) blocks three signals neurofibroma cells

Clapp

use to communicate with each other. "It's like getting three drugs for the price of one," Kent Robertson, MD, PhD, who is running the current clinical trial, said. In one dramatic example prior to opening the current phase II trial, a three-year-old patient with a severely compressed airway experienced a "profound opening of her airway" while being treated with imatinib for three months, according to Robertson. In the phase II trial, patients with serious plexiform neurofibromas are treated with oral imatinib for six months with the option to continue treatment for up to two years, if they are showing a benefit. In neurofibromatosis 1 (NF1), tumors grow slowly near nerves, blood vessels, the spinal cord, and the airway. Because of these sensitive locations, surgery is difficult and because of slow growth, these tumors do not respond to the usual kinds of cancer chemotherapy. NF1, a genetic disorder also known as von Recklinghausen disease, occurs in about 1 in 3,500 births and is characterized by café-au-lait spots; tumors under the skin; freckling under the armpits; and characteristic alterations in the iris of the eye.

NEJM publishes Miller's article

The positive results of the first nationwide clinical study showing the benefits of an antiangiogenic agent in breast cancer therapy were reported in the Dec. 27 issue of the *New England Journal of Medicine*. The study -- coordinated by the Eastern Cooperative Oncology Group (ECOG) and Kathy Miller, MD, the lead author -- with bevacizumab (Avastin) showed the biggest improvement in metastatic breast cancer ever reported in a chemotherapy-based clinical trial. It nearly doubled the time between initiation of chemotherapy for metastatic disease and progression of the breast cancer tumors. The study looked at paclitaxel (Taxol), which is one of the standard agents for metastatic disease, with and without the addition of bevacizumab. "This study not only achieved the longest progression-free survival in advanced disease but the therapy achieved that improvement without adding to the day-to-day treatment burden and with only minor increases in toxicity," Miller said. The study enrolled 722 women with metastatic disease from the United States, Canada, Peru and South Africa. Patients were randomized to one of two arms of the phase III study – paclitaxel alone or paclitaxel with bevacizumab. The results show that treatment with paclitaxel and bevacizumab increased the period patients went without progression of their disease from 5.9 months to 11.8 months. "The next step is to move Avastin into the initial treatment of breast cancer in hopes that it will prevent recurrence in the first place," Miller said. The first clinical study with bevacizumab in humans was done in 1997 by George Sledge, MD, a pioneer in the field of antiangiogenic research.

News briefs

Hoffmann to coordinate IU Simon Cancer Center's CompleteLife program

Mary Lynn Hoffmann has been named program coordinator of the Indiana University Melvin and Bren Simon Cancer Center's CompleteLife program. Hoffmann will oversee a program that delivers psycho-social counseling, complementary therapies, music and art in support of cancer patients and their families. The various services support the emotional, social, spiritual, and physical needs of adult patients.

10th Annual Amelia Project Retreat is Feb. 2

The 10th Annual Amelia Project Retreat is Saturday, Feb. 2 at University Place Conference Center. The meeting is designed to 1.) bring together scientists and clinicians working on basic research in breast cancer at institutions across Indiana; 2.) foster collaboration across institutional boundaries and enhance research through collegial sharing; and 3.) encourage and educate pre- and post-doctoral candidates. View the agenda. To register, send an e-mail to Nikkole@breastcare.org that includes your name and facility or institution by Jan. 25. You are also invited to submit an abstract for a poster presentation.

New grants

Brenda Grimes, PhD

"Epigenetic Changes in Centrometric Chromatin Cause Genomic Instability in Breast Cancer"
American Cancer Society Institutional Grant

Manjari Mazumdar, PhD

"Linking Chromatin Organization to Hematopoietic Development and Neoplasm: Modulation by a Molecular Motor KIF4"
American Cancer Society Institutional Grant

Robert Stahelin, PhD

"Mechanism of Chemotherapeutic Resistance of PKCn in Lung Cancer"
American Cancer Society Institutional Grant

Samy Meroueh, PhD

"Allosteric Regulation of the Interaction Between the Urokinase Receptor and Integrin with Small Molecules"
American Cancer Society Institutional Grant