New Initiatives Aim To Test More Cancer Drugs for Children

Since the 1970s, the mortality rate for children and adolescents with cancer has dropped by almost 50%, but the cure rate for pediatric cancer has plateaued in the past several years because there are relatively few new drugs being tested for childhood cancers, says Joseph Simone, M.D., professor emeritus of medicine and pediatrics at the Huntsman Cancer Institute at the University of Utah in Salt Lake City.

The number of cancer cases in children and adolescents each year is small—about 12,500—compared with the number in adults, and drug companies are reluctant to invest money in clinical trials for such a small population. Moreover, it can be difficult to enroll enough patients who meet specific enrollment criteria. When drugs are tested, there is usually a 5- to 10-year gap between the time they reach adults and the time they reach children.

“There is a consensus that there won’t be a rise in cure rates without new agents,” said Peter Adamson, M.D., chief of the Division of Clinical Pharmacology and Therapeutics at Children’s Hospital of Philadelphia.

The Children’s Oncology Group (COG) and its phase I consortium have conducted the lion’s share of childhood cancer clinical trials. But recently, a new group called POETIC (Pediatric Oncology Experimental Therapeutics Investigators) has formed with the goal of testing additional drugs for pediatric cancer in locales with major medical institutions not served by COG.

“COG has been an international leader in bringing many new drugs to the pediatric population, but some of us have just been frustrated at not being able to bring more new drugs to kids faster,” said Lia Gore, M.D., assistant professor of pediatric oncology at the University of Colorado Health Sciences.
Center in Denver and a founder of the new eight-institution consortium. “We are trying to complement COG’s work—not compete or duplicate their efforts—and are in active discussions with both COG and [the National Cancer Institute’s Cancer Therapy Evaluation Program (CTEP)],” said Gore. Specifically, the founders of POETIC want to increase pediatric enrollment in phase I trials, improve trial design, and enhance clinical and basic science knowledge gained from these trials, Gore said.

POETIC is working with drug companies to encourage them to test their investigational drugs in children and is beginning to make headway. It recently began testing the drug 17-AAG (geldanamycin) in osteosarcoma in two trials, and two combination trials are also in development. The group is planning trials with about six drugs in total for 2005, said Stephen Hunger, M.D., chief of pediatric hematology/oncology at the University of Florida’s College of Medicine in Gainesville. One is oxaliplatin (Eloxatin), a platinum compound, which is attractive for pediatric use because it has reduced ototoxicity and thrombocytopenia compared with cisplatin and carboplatin, which have been effective in many pediatric cancers.

Targeted Therapy Focus

POETIC is particularly interested in studying targeted therapies such as Iressa (gefitinib) and Erbitux (cetuximab) because a substantial proportion of pediatric malignancies, unlike adult cancers, are better characterized and more biologically homogeneous, with well-defined chromosomal translocations, molecular fusion products, or gene aberrations, said Gore.

Experts generally agree that most pediatric cancers are biologically different from adult cancers. Most pediatric cancer arise from mesenchymal tissue, whereas most adult cancer arises from epithelial tissue, said Frank Balis, M.D., clinical director of the NCI’s Center for Cancer Research. Typical childhood cancers include leukemia (about 75% of children with this disease have acute lymphoblastic leukemia); brain tumors and neuroblastoma; sarcomas, including osteosarcoma, Ewing’s sarcoma, and rhabdomyosarcoma; lymphomas (Hodgkin and non-Hodgkin); liver cancer; kidney cancer; retinoblastoma; and germ cell tumors.

While many pediatric oncologists concede that accessing new and even approved drugs for testing in their patients has been difficult, not everyone agrees that more clinical trial consortia are the answer. “POETIC is not necessarily meeting an unmet need,” said Gregory Reaman, M.D., COG chairman and professor of pediatrics at George Washington University/Children’s National Medical Center in Washington. He believes that there is no shortage of patients willing to enter a trial. COG is currently conducting 12 open studies and has 12 in development, he said. (In 2002, CTEP sponsored 28 pediatric phase I trials with 24 investigational drugs enrolling 193 patients, 15 phase II trials with 11 agents and 152 patients, and 7 phase III trials in approved drugs with 166 patients.)

Reaman chalks up the scarcity of pediatric cancer drugs to drug companies’ fears of unexpected adverse effects and accompanying bad publicity, as well as the small pediatric market. For Gore, part of the problem lies with the necessary regulatory and ethical guidelines...
that define children as vulnerable research subjects. Drugs need to be tested in adults first to establish safety and tolerability. “This means that by the time a drug reaches pediatric phase I trials, it is likely to be well into phase II and III testing in adults, or even be approved. The last thing we want to do is to rush a drug through, but at the same time, kids are out there dying who don’t have to die,” Gore said.

FDA Efforts

The U.S. Food and Drug Administration recently instituted two regulatory initiatives to counteract those forces. In January 2002, Congress passed the Best Pharmaceuticals for Children Act, which provides for a 6-month extension of marketing exclusivity for the entire product line of a drug if a sponsor agrees to conduct and submit results of pediatric studies, said Ramzi Dagher, M.D., medical team leader of the Division of Oncology Drug Products at FDA’s Center for Drug Evaluation and Research (CDER).

“Several labeling changes have been made already to some oncology drugs based on studies conducted under these agreements, and there are several other drugs for which studies are being conducted currently and others for which plans are being discussed between sponsors and the FDA,” he said. Some are for previously marketed drugs, and some are for recently approved or investigational drugs, Dagher added. More than 100 drugs have been approved by CDER for cancer, but only 15 have pediatric use information in their labeling—less than 50% of drugs commonly used to treat childhood cancers. “There have only been six submissions to the FDA for pediatric oncology indications in the past 20 years,” observed Steven Hirschfeld, M.D., Ph.D., also of the Division of Oncology Drug Products at FDA’s CDER.

The second initiative, the Pediatric Research Equity Act, is a mandatory program enacted in December 2003 that applies to any drug, whether it is new or already marketed and under review for a specific indication. “If the indication

is similar in children to adults, such as some sarcomas, leukemias and lymphomas, sponsors would be required to conduct trials and submit results of pediatric studies,” said Dagher.

A few months earlier in 2003, the Department of Health and Human Services identified an initial list of 12 approved drugs that “urgently” need pediatric testing, according to a statement by HHS Secretary Tommy Thompson.

The list grew to 20 by February 2004, and in the expansion, two older cancer drugs, vincristine and dactinomycin, were added to the list.

This is symptomatic of the larger problem, Gore said. “Vincristine has been used in pediatric oncology since the 1950s and 1960s. It will never be systematically tested because it is considered standard of care for many types of pediatric cancers, and no one would ever go without it in a randomized study. The story with dactinomycin is almost the same. These are old drugs that are important to standard therapy, but studies with them in children would add little to current knowledge,” she said. Resources should be devoted to newer agents, she asserted.

“Since the FDA initiatives, the situation has improved somewhat,” Adamson said, and others agree. “But the challenges in pediatric oncology are deeper than getting new drugs to trials,” he said. “One problem is that there has never been a systematic, forward-looking preclinical effort to look at new agents,” Adamson said.

Preclinical Research

Such a program has just been initiated. On September 30, the NCI approved 5 years of funding to develop preclinical models of childhood cancers to determine which drugs are most likely to be effective to treat them. “Researchers will develop pediatric xenograft models using SCID mice to systematically screen drugs against pediatric tumors, develop in vitro cell lines, mouse models, and test them against a few conventional drugs to calibrate the system and provide a baseline for combination treatments,” said Malcolm Smith, M.D., Ph.D., of NCI’s CTEP.

Balis is developing microarrays for 17 different childhood tumors and receptors and will screen targeted drugs such as gefitinib and Tarceva (erlotinib) to determine “if it is rational to use them in children.”

Gore and Balis both said that the current strategy in cancer drug development—away from random screening and indiscriminate killing of rapidly-growing and dividing cells and toward targeting proteins at the cellular level—should guide future testing of pediatric cancer drugs.

“We need better strategies to define the biologic characteristics of patients and tumors for which new therapies are most appropriate, as well as to elucidate mechanisms leading to the malignant phenotype, and novel trial design is needed for the newer, molecular targeted therapies,” Gore said.

—Vicki Brower

Pediatric Research Equity Act

The Pediatric Research Equity Act, passed by Congress in 2003, gave the U.S. Food and Drug Administration the authority to require drug manufacturers to perform pediatric testing on certain products.

In October of 2002, a U.S. district court ruled that the FDA lacked sufficient statutory authority to require pediatric studies and prevented FDA from enforcing the requirements that were originally mandated in a 1998 regulation known as the “pediatric rule.” After the court ruling, the FDA sought a congressional mandate that would give the agency the authority to require such studies.

The full text of the act is available at http://www.fda.gov/opacom/laws/prea.html.