Pediatric Drug Trials Facing Some Obstacles

At a recent meeting of a U.S. Food and Drug Administration advisory panel, experts expressed a mixture of hope and disappointment after reviewing early attempts to conduct federally mandated studies of newly approved oncology drugs in children.

“The frustration in the room was really not so much with the pace of the studies as it was with the lack of early communication in the planning and consideration of the studies,” said Gregory Reaman, M.D., chairman of the FDA’s Oncologic Drugs Advisory Committee’s pediatric subcommittee.

At the meeting last month, industry representatives presented the status of pediatric studies for Clolar (clofarabine) in refractory leukemia, Neulasta (pegfilgrastim) for neutropenia, and Kepivance (palifermin) for oral mucositis.

Clofarabine was granted accelerated approval for use in children in December 2004 and, as part of the approval process, is undergoing postmarketing studies to verify and better document the drug’s clinical benefit. The drug’s manufacturer, Genzyme Corp., is now trying to design phase I and II trials to establish the best combination regimen that would then be used in a phase III efficacy trial, said Rekha Abichandani, M.D., medical director of clinical research at Genzyme Corp.

Amgen, the maker of the other two drugs already approved for indicated use in adults, has faced its own difficulties in the execution of studies designed in 1999 and 2000 with the help of the agency.

Pediatric studies, such as these involving drugs for which the companies are seeking FDA approval, are mandated by a federal law that passed in 2003, called the Pediatric Research Equity Act. Another law, the Best Pharmaceuticals for Children Act (BPCA) of 2002, helps to promote studies to better understand or improve on therapies that are already approved and on the market. That law offers companies a 6-month patent extension for conducting follow-up studies in children, although that incentive is not there for many potential test drugs that are already off patent. So, if companies decline to study the agents, the National Institutes of Health can pick up the ball, contracting out with an investigator group such as the Children’s Oncology Group.

Both laws grew out of the FDA’s Pediatric Rule, a regulation published in 1998 that required companies to generate more pediatric data.

In 2002, a U.S. District Court ruled that FDA had exceeded its authority with the Pediatric Rule. However, Congress then stepped in, codifying the rule with passage of BPCA and the Pediatric Research Equity Act (PREA). The early pediatric studies conducted by industry were initiated under the Pediatric Rule, whereas more recent ones are the product of PREA compliance.

“From a pediatric advocacy perspective, this law has been a success. It has removed many of the perceived barriers to conducting trials in children,” said Richard Gorman, M.D., the immediate past chair of the American Academy of Pediatrics’ Committee on Drugs. AAP was integral in passage of the legislation.

Obstacles

But compliance with these regulations can prove difficult. At the October subcommittee meeting, Abichandani said that Genzyme has already faced a major obstacle in designing its studies.

“There are no standard therapeutic options for these patients, making it hard to design a comparison study,” she said.

FDA officials also have expressed concerns that the proposed design of the clofarabine study will not be able to establish enough of a clinical benefit over the combination regimen without the drug, she said.

Although it is fortunate that childhood cancers are rare, it also means that researchers have a relatively small pool of potential trial participants. Companies have also found themselves in competition with other trials, often of yet unapproved drugs or other interventions that were considered more directly relevant to survival than that offered by adjunct therapies, said representatives from Amgen and Genzyme.

All of these factors lead to one result. The pediatric studies often end up taking much longer to accrue patients and therefore complete, often years beyond what it would take to complete a comparable in adults.

“If it takes too long to get that data, it may no longer be useful,” said Reaman.

Industry researchers are not the only ones facing difficulty in conducting pediatric studies on oncology drugs. A study to improve on the safety and efficacy in children with the combination of actinomycin-D and vincristine in children is under way by researchers with the Children’s Oncology Group. The study is funded through the BPCA.

However, before clinical trials can begin, the researchers have had to overcome many technical difficulties because of the complexity of administering the therapy in children and the many unknowns about their pharmacokinetic properties in children, especially infants, said Jeffrey Barrett, Ph.D., an associate professor of pediatrics at the Children’s Hospital of Philadelphia.

Evolving Process

Difficulties aside, FDA officials agree that the law has been important in getting such pediatric research off the ground. “If we don’t have studies, we don’t accrue data,” FDA’s Lisa Mathis, M.D., said at the meeting. “That was a fact of life for us before this legislation.”

The laws have driven new research in pediatric therapies, but there is still a lot of work to do in making the process work smoothly, said Reaman, who chairs the Children’s Oncology Group and is a professor at the George Washington University School of Medicine.

Too much of the early research design and implementation has been developed
without input from the pediatric cancer community, he said. However, the process is still new and evolving, he added.

The FDA only recently released draft guidance, the preliminary step to providing the industry with an outline for compliance with PREA. The agency now has to review and incorporate comments on the guidelines from researchers, industry, and other stakeholders.

There have also been several changes in leadership both within the FDA and industry that have interrupted progress on this research, said Reaman.

FDA officials acknowledge that their processes need to be further refined, but the agency has vowed to work closely with members of the oncology community.

“Look at this [process] as your friend, not your enemy,” Richard Pazdur, M.D., director of the Office of Oncology Products within FDA’s Center for Drug Evaluation and Research, urged the subcommittee members.

Still, some members expressed concern that the process, although it may produce new and valuable data, could also lead to delays in their access to new drugs. Referring to the presentation of existing adult data on clofarabine, one member said it was clear to him that the drug was active and he wouldn’t want to wait for clinical trials to use it in pediatric patients who were not responding to other therapies.

However, discussing these concerns will ultimately help set a better tone, said Reaman.

“The pediatric oncology clinical investigators are very interested in working with the pharmaceutical industry. The FDA is very interested in both of us working together to expedite and facilitate the drug development process in pediatric cancer,” he said.

However, pediatric oncologists have to be realistic in what they expect to come out of this process, said Reaman.

“Although cancer is the leading cause of death from disease in pediatrics, there are many other diseases which although perhaps not fatal have serious implications for a very large part of the American public. We recognize that there is a prioritization process.”

—Joel B. Finkelstein