

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Current Challenges in Pediatric Drug Development

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H&O What are the main challenges in developing drugs for children?

PA As the biopharmaceutical industry does not generally develop drugs specifically for childhood cancers, one of our first challenges is to determine which drugs being developed for adults have relevance in pediatrics. A critical step in prioritizing amongst these agents requires an understanding of the key targets in pediatric tumors and an exploration of whether there is potential for efficacy of select agents. Even after drugs that are potentially relevant to pediatric tumors are selected, childhood cancer drug development faces additional challenges such as developing formulations for children of different ages and studying a drug's clinical pharmacology across a spectrum of ages.

A complementary challenge involves the development of new agents against targets that are found primarily, if not uniquely, in childhood cancers. Underlying this challenge is the reality that the pharmaceutical industry has no economic incentive to develop an agent specifically for a childhood cancer. It is important to point out, however, that there are economic incentives to studying drugs that are being developed for adults with cancer in children.

H&O What is the current status of investigational pediatric drugs?

PA Over the last 5–10 years, the biopharmaceutical industry has been paying more attention to pediatric cancer drug development. Most pharmaceutical companies have engaged the pediatric oncology community to

determine how to best study drugs that are in clinical development for adults in children. This is the result of recent legislative initiatives, including economic incentives for industry, which have changed the landscape and impacted both how and when industry interacts with the pediatric oncology community.

Unfortunately, funding has not kept pace with the increasing regulatory requirements for conducting clinical research and is now one of the main limitations of pediatric clinical cancer research. The cornerstone of childhood clinical cancer research—the cooperative group structure supported by the National Cancer Institute (NCI)—is inadequately funded to fully carry forward its research mission. All childhood cancer research centers thus look for alternative sources of funding—philanthropic and institutional—to help support the national clinical research effort.

H&O How do clinical trials in children differ from those in adults?

PA For pediatric clinical investigations, federal regulations afford additional protections to children enrolled in clinical trials. Although the requirements one must meet in order to proceed with clinical investigations in children are greater than those for adults, these challenges are not necessarily difficult to address. One has to pay close attention to the trial design, which in most cases will not be a simple mirror image of adult clinical trial designs. For the majority of childhood clinical cancer research, there has to be a prospect of direct benefit to the child enrolled in a study.

H&O What factors influence pediatric clinical trial participation?

PA As a subspecialty, pediatric oncology is rooted in clinical research. Because the vast majority of children with cancer are treated at academic medical centers, most families are offered the opportunity to participate in clinical research at the time of initial diagnosis. For a child

and family who are newly diagnosed, the explanation of the research process includes information about the child's diagnosis, disease, treatment, and prognosis. The discussion about participation in clinical research thus can occur at a time of overwhelming emotion.

What several recent phase III studies have done is stage the clinical research process for newly diagnosed patients. Initial research focuses on tumor specimen acquisition and biologic studies with the initial administration of standard therapy. Following this, if there is a randomized question to be asked or a biologic risk stratification that needs to occur, a second consent is obtained at a later time. This latter consent details the next phases of the study, and the extra time affords families the opportunity to further understand the research questions.

H&O Are there any noteworthy pediatric studies that are ongoing?

PA There are many important studies underway, but with respect to new agent development, several come to mind. One study, being conducted through the Children's Oncology Group Phase I Consortium, is using an antibody against the insulin-like growth factor receptor (IGFR). There is laboratory evidence that the IGFR1 pathway is an important pathway in a number of pediatric cancers, and anti-IGFR-1 antibodies have shown early indications of efficacy in children with Ewing's sarcoma. The IGFR1 antibody story is an excellent example of how an agent being developed for adult indications yielded a strong and early clinical signal in a childhood cancer.

Colleagues at the Children's Hospital of Philadelphia have recently identified the genetic basis of a rare form of neuroblastoma—familial neuroblastoma. Drs. Yael Mossé and John Maris found that the genetic defect (mutations in ALK) is not only the cause of familial neuroblastoma but may well be responsible for a subset of sporadic cases. Fortunately, there are agents in the early clinical pipeline that target ALK, and we are working with the NCI and industry to quickly move an inhibitor into pediatric clinical trials.

In addition to clinical studies, there is now an international collaboration for preclinical testing of new agents through the Pediatric Preclinical Testing Program (PPTP). A recent finding from the PPTP suggests that aurora A kinase may be an important target for select pediatric malignancies, and thus we have been able to move an aurora A kinase inhibitor into early phase testing for children.

H&O What can the pharmaceutical industry, FDA, and medical community do in order to progress pediatric drug development?

PA I think that the earlier a drug development plan is discussed between leaders in pediatric cancer drug development and the biopharmaceutical industry, the more efficient and effective the process will be. We should be having these discussions when companies are planning to enter clinical trials in adults and be prepared to initiate pediatric trials when the data supports doing so. This can be as early as when finding a biologic effect in an adult phase I trial and certainly upon completion of adult phase I testing.

It is also essential to sustain the current incentive program of 6 additional months of exclusivity for pharmaceutical companies that engage in conducting appropriate pediatric clinical trials for new agents. This has been the most effective incentive for pediatric drug development yet.

What will help in the future is not solely in the control of the biopharmaceutical industry. Currently, drugs are primarily labeled for pathologic indications—breast cancer, prostate cancer, and so forth. These types of cancers do not occur in children and therefore a company developing a drug for such indications is not required to study that drug in children. However, when we reach a time when a drug can be labeled based on a molecular pathway as opposed to a pathologic diagnosis, we will be able to extend the requirement that companies pursue pediatric clinical trials. This will not only be an advance for the medical oncology community but for the pediatric oncology community as well.