ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Drug Development for Rare Cancers in Children

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H&O How is a rare cancer defined?

LG Approximately 1.6 million cases of cancer are diagnosed each year in the United States. The US Food and Drug Administration designates an orphan disease as one with an incidence of less than 200,000 cases per year. Similarly, in the European Union, regulatory authorities define a rare cancer as one with an incidence of less than 5 or 6 per 100,000 person-years. Many cancers are therefore considered rare. In the adult population, rare cancers include sarcomas and several types of brain tumors. Approximately 16,000 children are diagnosed with cancer each year in the United States. All pediatric cancers can therefore be considered rare.

New technologies are allowing the identification of "micro-rare" diseases based on distinct molecular and biologic underpinnings. For example, there was previously a single diagnosis for lung cancer. Then we divided that into 2 different kinds of lung cancer: small cell and non–small cell. Now within these cancer types, there are numerous subclasses and sub-subclasses based on molecular abnormalities and gene mutations. So even lung cancers can now be rare diseases, although they affect hundreds of thousands of people each year.

H&O Do clinical trials for rare cancers require any design modifications?

LG It depends on the goal of the trial. For example, a trial in a rare population could use an accelerated dose-escalation design or might use a continuous reassessment model to predict risk of toxicity or to determine when a patient can advance to the next dose level, thereby exposing fewer patients to potential side effects while sparing a large number of patients treatment at less effective doses. Stratification based on molecular and biologic characterizations to subdivide cohorts can make trials more efficient in terms of patient allocation.

H&O What are the barriers to implementing clinical trials for rare cancers?

LG There are many. It can be difficult to obtain financial support. Clinical trials are expensive to run. Potential sponsors hope to obtain a return on their investment, which might be limited in a disease setting with a relatively small population. Trials for rare cancers might require a longer enrollment period and a larger number of sites to identify patients with specific molecular and biologic characteristics.

H&O Are there any recent insights into the biology of rare cancers?

LG In the past 10 years, technological advances have shown that many cancers have unique biologic characteristics, almost a genetic or molecular "fingerprint." The discovery of a gene aberration or an abnormal protein can provide insight into the cancer's origin. This information suggests that more cancers are associated with genetic predispositions or might be related to other medical conditions. Medical conditions can overlap, and sometimes cancer is part of that process. For example, some cancer predisposition syndromes are associated with

developmental abnormalities, sensitivity to sun exposure, and inability to repair wounds or skin damage. Some people with genetic syndromes are also "hypersensitive" to DNA damage, so we must be careful to treat their cancers appropriately to minimize the chance of causing a second cancer. We might avoid certain types of chemotherapy or radiation, for example.

H&O Do these patients benefit from molecular profiling?

LG Under some circumstances, patients actively benefit on a daily basis. Some cancers have molecular drivers that can now be targeted, allowing us to either greatly reduce exposure to cytotoxic chemotherapy or eliminate it altogether. For example, we might treat patients differently if we know they have a molecular alteration that increases their risk of toxicity from particular medications. In those cases, it may be possible to treat with lower doses of drugs to obtain an equivalent effect without increased toxicity.

It should be noted, however, that identification of molecular abnormalities does not always define the treatment path. We can characterize a cancer much better now at the molecular level, but we are still learning how to apply that information in many cases. It will be necessary to collect and study these data in order to develop new drugs for particular targets.

H&O What is the focus of your research?

LG My primary focus has been developing drugs for cancer in children and adults, primarily in the phase 1 setting but also in some disease-specific, phase 2 trials. My main clinical interest is leukemia, but I have also done work in sarcomas and brain tumors. Our work has led to the use of tyrosine kinase inhibitors in children with chronic myeloid leukemia and Philadelphia-positive acute lymphocytic leukemia (ALL), and most recently to the approval of blinatumomab (Blincyto, Amgen), a bispecific T-cell engager immunotherapy, in children with relapsed and refractory B-lineage ALL. We are constantly learning how to optimize treatment for refractory disease, and I hope our current work will help reduce the burden of conventional multi-agent cytotoxic therapy for some patients who may be cured with less therapy, therapy that is less intense and/or given for a shorter course.

H&O Has your research provided any insight into drug development for rare cancers?

LG We have become better at bringing drugs to the forefront for children with cancer. The first time I designed a multicenter clinical trial, in 2001 to 2002, children with brain tumors or leukemia were usually excluded from phase 2 studies for safety reasons. It was thought that drugs should be tested in children with solid tumors before they could be tested in children with brain tumors or leukemia. We purposefully fought this convention and designed a study with 3 cohorts: solid tumors, brain tumors, and leukemia. This approach was not associated with any undue harm in that trial, and we learned a lot in the process. It is now accepted that children with brain tumors or leukemia can be included in the first trials of a new agent, provided there is a good biologic rationale and potential for benefit. Excluding these children from enrollment can harm them by blocking access to effective therapy. Enrollment of children in a clinical trial can also provide information on the drivers of the disease. Safety is always a primary concern, and careful attention is required. These trials should include investigators with experience managing complex pediatric diseases, as well as a multidisciplinary team to support and manage both the patients and the trial demands.

> New technologies are allowing the identification of "micro-rare" diseases based on distinct molecular and biologic underpinnings.

H&O Do you have any suggestions on how to translate laboratory work into early-phase clinical trials?

LG The key word is "partner." Clinicians, translational scientists, and clinical trialists must partner with basic scientists. There must be regular, frequent conversations about laboratory discoveries, such as the identification of new genes.

H&O What are some promising areas of research?

LG There are approximately 900 to 1000 new drugs in clinical trials each year. Exciting discoveries are being made regarding the molecular underpinnings of diseases, in particular, understanding gene mutations and abnormalities. There is exciting research evaluating how to harness the immune system to fight cancer. Several small molecule inhibitors look promising.

H&O What type of work is done by the Experimental Therapeutics Program?

LG The Experimental Therapeutics Program at Children's Hospital Colorado is designed to bring drugs to children with difficult-to-treat diseases as quickly and safely as possible. It also aims to answer basic biological questions. The program focuses on phase 1 and some phase 2 trials. The goal is to not unnecessarily exclude patients from participation in clinical trials when they have the potential to benefit and there is the potential to learn about the disease.

Disclosure

Dr Gore serves as an advisor to Amgen for pediatric immunotherapy development and on the Data Safety Monitoring Boards for Celgene and Novartis.

Suggested Readings

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