

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Developing Drugs for Pediatric Malignancies



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H&O What are some notable areas of progress regarding drug development for pediatric cancer patients?

PA In the past, pediatric patients with Philadelphia chromosome–positive acute lymphoblastic leukemia (ALL) had very poor outcomes when treated with chemotherapy alone, and the use of hematopoietic stem cell transplantation (HSCT) offered only modest survival benefit. Over the decades, we have been looking for ways to improve outcomes for these patients, who historically had a 5-year survival of only 20%. Treatment of chronic myelogenous leukemia (CML) was revolutionized with the development of tyrosine kinase inhibitors (TKIs) that target the BCR-ABL1 fusion protein produced by the Philadelphia chromosome, such as imatinib (Gleevec, Novartis), dasatinib (Sprycel, Bristol-Myers Squibb), and nilotinib (Tasigna, Novartis). Fortunately, we have been able to leverage the advances from CML and apply them to childhood ALL. The Children's Oncology Group (COG) AALL0031 trial showed that the addition of imatinib to intensive chemotherapy did not cause increased toxicity, and 3-year event-free survival rates were more than double those of historic control data. We continue to study second-generation TKIs for children with Philadelphia chromosome–positive leukemias. Overall, TKIs in development for adults may have a significant impact for small subpopulations of children with certain cancers.

H&O What factors are behind the slowing of progress in recent years?

PA Between 1970 and the end of the 1990s, survival rates for pediatric cancer patients steadily improved in a near lin-

ear manner. What is quite remarkable is that all of the drugs used to treat most childhood cancers were developed and approved in the 1950s, 1960s, and 1970s. Even though we had everything in hand by the 1970s, improvements did not happen overnight, but instead over the course of 30 years. Today, however, it is likely that we have gotten as much mileage as we can expect out of drugs that are 30–50 years old. For the most part, we have intensified therapy in the subpopulations of children whose outcomes were unacceptable, and for most diseases we have pushed the principle of dose intensification as far as it can go.

Since 2000, there has been an increase in the number of new agents developed for adult cancers. The relevance of the priority targets in adult cancers does not necessarily align with the relevance in pediatric cancers. Our challenge is in identifying new agents in the clinical development pipeline for adult malignancies that have potential to improve the outcome for childhood cancer. In a number of cases, we still have a limited knowledge regarding key targets for childhood cancers, as well as in our ability to access new agents in a timely manner.

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

PA We have been successful in studying a broad range of new drugs in early-phase clinical trials. Among the most promising are agents that have activity in adult tumors and also target oncogenes believed to be important for pediatric tumors. For instance, drugs that target anaplastic lymphoma kinase (ALK) appear to be active in anaplastic large cell lymphomas (ALCL), which comprise approximately 15–20% of childhood lymphomas. Crizotinib (Xalkori, Pfizer) appears to have major activity

for children with relapsed and refractory disease. Further, monoclonal antibodies such as brentuximab vedotin (Adcetris, Seattle Genetics), which targets CD30, also appear to be highly efficacious in children with ALCL.

There is also mounting evidence suggesting that there are subpopulations of children with ALL who might benefit from other signal transduction and pathway inhibitors, but it will certainly not be across the board. The good news is that some of the new drugs are being evaluated in frontline clinical trials. We are looking at bortezomib (Velcade, Millennium Pharmaceuticals) in an upfront study in children with acute myelogenous leukemia (AML), as well as sorafenib (Nexavar, Bayer) in children with AML who have FLT-3 internal tandem duplications.

H&O What are the major challenges surrounding clinical trials?

PA Fortunately, in the COG, more than 90% of children with cancer are treated at one of our COG member institutions. COG covers the United States and Canada, Australia, New Zealand, and select centers elsewhere internationally.

Research is embedded in pediatric oncology. Of all newly diagnosed children, approximately 60% are enrolled on clinical trials, so a very high fraction of children participate in research. That is the good news. One major challenge concerns the financial changes that are occurring. The costs of conducting clinical research are increasing at a time when the National Cancer Institute (NCI) budget is decreasing. Childhood cancer research is almost entirely dependent on federal research dollars, in contrast to a significant component of medical oncology research that is also supported through industry contracts.

Among the scientific challenges of note is likely the development of biomarkers. Not only is such a development scientifically difficult, the regulatory requirements surrounding biomarker utilization are also increasing.

As importantly, advances made in childhood cancer have not been realized uniformly around the globe. Fiscal restrictions and limited access to important drugs and clinical trials are common in other regions of the world with fewer resources.

H&O How have legislative initiatives affected the drug development and treatment landscape?

PA Legislative initiatives in the United States have had a major impact on the lives of children. The Best Pharmaceuticals for Children Act (BPCA) offers economic incentives for companies to study medications in children, and the Pediatric Research Equity Act (PREA) requires such studies in specific situations. However, their impact

on childhood cancer drug development has been more modest. BPCA and PREA address only how cancer drugs developed for adults should be studied in children. A major limitation is that drugs are labeled for cancer on the basis of a pathologic indication, for example, colon cancer or lung cancer, even though the drug target for a common adult cancer might be highly relevant to a pathologically distinct pediatric cancer. Thus, PREA has no effect on childhood cancer drug development because companies regularly obtain waivers from this requirement.

The European Medicine Association established a program that falls under the rubric of Pediatric Investigation Plans, or PIPs. An unintended consequence of such legislation appears to be a delay in the initiation of early-phase clinical trials. PIPs require review and approval of a complete development plan, often including phase III trials, before pediatric trials in Europe can start. As drug development is increasingly global, these delays impact us in the United States. Making commitments to phase III studies before the drug has been tested in early-phase clinical trials in children is counterproductive; whether a drug should be fully developed, and, if so, how, is determined by results from early-phase studies. As such, companies delay the start of phase I investigation while trying to develop complex phase III development plans without key data. This approach is draining resources, as companies struggle to come up with these plans and will often delay the start of pediatric studies until their plans have been approved.

H&O What is being done to overcome these legislative obstacles?

PA Last year, the Creating Hope Act was passed and signed into law. It creates an incentive for companies that embark on developing a drug for a pediatric life-threatening indication as the first indication. That incentive is in the form of a priority review voucher at the US Food and Drug Administration (FDA) that is transferable to another drug developed and submitted to the FDA by the same company, which offers the potential for greater economic return. Right now, it is in a pilot phase, where the initial drugs that apply and are successful will be evaluated to see what the actual impact is going to be. This is an important piece of legislation, and it is the first Congressional effort to address the profound scarcity of pediatric cancer drugs.

H&O What are some areas of noteworthy research?

PA Another recent advance is the success of an immunotherapeutic approach in children with high-risk neuroblastoma. The outcome for children with high-risk neuroblas-

toma has been poor, with more than half of pediatric patients succumbing to their disease despite intensive multimodality therapy. A study conducted by the COG showed improved outcomes when an immunotherapeutic approach was added to intensive multimodality therapy. This strategy has now become standard of care in the frontline setting.

With regard to hematologic malignancies, there is a lot of excitement over early data, for both immunotherapy and cellular therapies. Blinatumomab is a bi-specific antibody that binds CD19 and CD3, thus activating T cells in close proximity to CD19-positive lymphoblasts. Early data in adults and children show that this approach has efficacy in the refractory setting. Anti-CD19 chimeric antigen receptor (CAR) therapies have also produced clinical responses in CD19-expressing malignancies. Positive early data in children with refractory leukemia have emerged from the Children's Hospital of Philadelphia and the University of Pennsylvania. Immunotherapy and cellular therapies in hematologic malignancies are setting the stage for potential future studies in solid tumors that extend beyond neuroblastoma.

H&O What are the biggest remaining challenges?

PA We need to gain a thorough understanding of the key targets across the spectrum of childhood cancers. The early data will not hold all the answers. In fact, for a significant number of cancers, there will not be a clear

druggable target that emerges. Thus, the challenge is to continue research to try and understand what the relevant targets are, and then develop therapeutics against certain targets that are not yet druggable.

H&O What do you think the future holds?

PA Moving forward, I think we will continue seeing important discoveries in certain ultra-rare diseases, as well as in small subsets of the more common childhood cancers, including childhood ALL, childhood AML, and medulloblastoma. We will be identifying subpopulations of children who may benefit from existing or targeted therapies in development. A lot more discovery work remains. As diseases that are already considered rare are divided into smaller groups, designing studies that can efficiently answer the questions of efficacy will become increasingly important.

Suggested Readings

Vassal G, Zwaan CM, Ashley D, et al. New drugs for children and adolescents with cancer: the need for novel development pathways. *Lancet Oncol.* 2013;14:e117-124.

Norris RE, Adamson PC. Challenges and opportunities in childhood cancer drug development. *Nat Rev Cancer.* 2012;12:776-782.

Adamson PC. The Children's Oncology Group's 2013 five year blueprint for research. *Pediatr Blood Cancer.* 2012. [Epub ahead of print]

Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group study. *J Clin Oncol.* 2009;27:5175-5181.