

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Challenges in Drug Development for Children



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H&O How common is cancer in children?

PA In the United States, there are approximately 14,500 new cases of cancer diagnosed each year in children from birth up to age 19 years. Approximately 1800 to 1900 of these patients will die from the disease. Despite the progress that has been made in the treatment of these patients, death from cancer remains the leading cause of death from disease in children. There is an urgent need to bring new therapies to this population.

When looking at incidence data, it is important to note that the definitions of child vary. For example, the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) includes patients from birth to 19 years. Pediatricians generally consider childhood to end at age 12 years and adolescence to begin at age 13. Most children with cancer are treated at children's hospitals, which often accept newly diagnosed patients up until their 21st birthday.

Children, adolescents, and even the young adult population experience a distinct set of cancers that may require unique treatment approaches. One of our challenges is how better to bridge the pediatric-adult divide, and improve care for adolescents moving into young adulthood.

H&O Do cancers tend to manifest differently in children vs adults?

PA The types of cancers that occur in children differ from those in adults, and therefore manifest differently. In adults, most cancers are carcinomas, and prognosis can improve with early detection. In children, carcinomas are

rare. The more common cancers in children include the hematologic malignancies (leukemias, lymphomas), brain tumors, tumors of the peripheral nervous system (neuroblastoma), kidney tumors (Wilms tumor) and sarcomas (tumors of the muscle, bone, or soft tissue).

In most cases of childhood cancer, symptoms lead to a diagnosis in a relatively short time. Hematologic malignancies tend to present acutely. For certain pediatric solid tumors, parents might notice an abdominal mass that turns out to be malignant. A more indolent presentation might be seen with bone tumors. Bone pain, lumps, and bumps are relatively common in kids, and might not raise suspicion of cancer for some time.

H&O Are any treatment-associated adverse events unique to children?

PA The frequency and severity of side effects can differ between children and adults. One of the more serious adverse events in infants and toddlers involves their susceptibility to radiation and other types of therapy that can injure the developing brain. Young children are more susceptible to deleterious effects from radiotherapy than older children and adults. However, children's overall good health may make them more tolerant to some of the other common toxicities of classic cytotoxic chemotherapy, predominantly, myelosuppression.

H&O What types of acute and long-term morbidity are seen in children with cancer?

PA Approximately 80% of children undergoing treatment for high-risk cancers experience severe, life-threatening,

or fatal side effects at some point during their treatment. These high-risk cancers include, but are not limited to, certain types of leukemias, neuroblastoma, brain tumors, and sarcomas.

Unfortunately, acute toxicities are only part of the challenge. Among children who are long-term survivors, more than 50% experience lifelong consequences from treatment. The side effects for survivors are diverse and dependent upon a number of factors, including therapeutic modalities used, types of drugs and doses of drugs administered, and age of the child undergoing treatment. For example, a significant number of survivors experience cardiac toxicity and are at high risk for heart failure as young adults from treatment with anthracyclines. Hearing loss is a major issue associated with high doses of cisplatin, which are often used in children with high-risk neuroblastoma and other malignancies. Adolescents who receive corticosteroids as part of their leukemia treatment have a high risk of avascular necrosis and might require joint replacements during their teenage and early adult years. Ultimately, all organ systems are potentially impacted by treatment for cancer.

H&O What characteristics in children can impact drug disposition?

PA Drug disposition in children can differ modestly from that in adults. At the simplest level, it is necessary to scale drug dosages to body size. In addition, developmental changes occur from infancy through adolescence. The most rapid period of change is during the first 2 years of life, when different hepatic enzyme systems may be expressed, renal function matures, and gastric function changes. Differences in drug disposition are not necessarily easy to predict, but there are some general principles. Clearance of many drugs tends to be somewhat faster in children than adults. Historically, children have been able to tolerate higher exposures to cytotoxic chemotherapy. (This observation may be at least partially attributable to the different treatment goals in children vs adults, which lead us to push exposures higher in children.) Children have fewer comorbidities than adults, so it is possible to administer more intensive therapy. A common expression is that children are not small adults. Although that is true, the experience in adults is very informative for determining drug disposition in children.

H&O Most clinical trials enroll either children or adults. Is this a necessary strategy?

PA It is not a necessary strategy. There are, however, special protections afforded to children participating in research. The US Food and Drug Administration

(FDA) and the US Department of Health and Human Services identify children as a vulnerable population. It is generally not difficult to meet the requirements involved in enrolling children in clinical trials, but it requires an extra layer of thought and review. The general principle is that if the research entails greater than minimal risk, which occurs with most types of therapeutic research in cancer, there has to be a prospect of direct benefit to the child participating in research.

For certain diseases and certain drugs, it makes sense for adolescents to participate in trials that are enrolling adults. For younger children, however, specific studies

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are required because of the developmental changes in this population, as well as the distinct types of cancer that tend to occur. In general, children receive better care in a pediatric setting accustomed to caring for children of all ages. Many cancer centers that provide excellent treatment primarily for adult patients may not be able to do so for children. Studies that enroll both adults and adolescents could lead to drug approvals that encompass a lower age limit than currently seen for most cancer drugs.

H&O What are the challenges in drug development for children?

PA Although childhood cancer is sometimes referred to as one disease, pathologically, it encompasses more than 140 different diseases. As we learn more about the molecular underpinnings of these diseases, it will be possible to further divide them into smaller subgroups. Childhood cancers thus consist of a large collection of rare and ultra-rare diseases. We are fortunate that frontline therapy produces sustained survival or cures in a relatively high proportion of children. What that means, though, is that early drug-development studies are suitable for a relatively small subpopulation. The economic models for industry to develop drugs in this setting are therefore lacking. Although legislative efforts have tried to address

these challenges, industry's footprint in developing new therapies for children is very small.

The advances in survival have come at a high cost. The main challenges are acute and long-term toxicity. We have to work to maintain good outcomes while decreasing toxicity by integrating new agents. Another important challenge is that the investment in childhood cancer research is too small. Research into molecular pathways and targets, and how to interrogate those targets, is not currently funded at a level that would accelerate advancements.

H&O What are some new molecular pathways that could be used for children?

PA The mutational burden of childhood cancers is lower than that for adult cancers. For example, across the spectrum of cancers, melanoma has a very high mutational burden, whereas the childhood cancers generally are clustered at the low end. The low level of mutations may impact the therapeutic approaches. One example

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is whether checkpoint inhibitors, which are effective for certain adult cancers, will have any meaningful impact for childhood cancers.

When aberrations are found in a pediatric malignancy, the molecular change is often fundamental to the malignant process. For example, many childhood cancers are driven by fusion oncoproteins, which result from translocations. A small number of fusion oncoproteins involve targets that are currently druggable, such as kinases. For a number of childhood cancers, however, although the molecular basis has been recognized for decades, no methods yet exist to target the oncoprotein.

One of the more promising areas for therapeutic development has been for children with acute lymphoblastic leukemia (ALL). Historically, for children with ALL driven by the Philadelphia (Ph) chromosome, which accounts for 3% to 4% of children with ALL, outcome was poor. This outcome was dramatically impacted with the advent of imatinib (Gleevec, Novartis Oncology), which increased 5-year survival from approximately 25% to 75% when incorporated with cytotoxic therapy.

As part of the TARGET (Therapeutically Applicable Research to Generate Effective Treatments) initiative, a program supported by the NCI, investigators have identified a larger subset of children who may lack the Ph chromosome, but whose leukemia has a genomic signature that is almost identical to that of Ph chromosome-positive ALL. This type of leukemia has been termed Ph-like or BCR/ABL-like ALL. For Ph-like ALL, a number of fusion oncogenes drive the leukemia, which may be targeted by current drugs. In an ongoing study, we are screening children with high-risk ALL to identify those with Ph-like ALL. When there is a drug that may target a pathway, we are studying whether the addition of that drug to cytotoxic chemotherapy can improve the outcome, as was seen with imatinib. Currently, there are 2 such drugs, dasatinib (Sprycel, Bristol-Myers Squibb/Otsuka) and ruxolitinib (Jakafi, Incyte), under study for this population. It is hoped that the use of these treatments will improve outcome for a larger subset of children with high-risk leukemia. Notably, Ph-like ALL is more common in adolescents and young adults, so these discoveries are extending beyond the traditional pediatric population.

H&O Are there any other promising therapies?

PA Anaplastic large-cell lymphoma (ALCL) accounts for approximately 15% of childhood lymphomas. It is driven by a mutation in the anaplastic lymphoma kinase (*ALK*) gene. Crizotinib (Xalkori, Pfizer Oncology/EMD Serono), which was initially developed for patients with non-small cell lung cancer, is a very potent ALK inhibitor. Studies are now showing that crizotinib produces a high response rate in children with ALCL. The antibody brentuximab vedotin (Adcetris, Seattle Genetics), which targets an antigen that is highly expressed in patients with ALCL, is also highly effective in children with ALCL. In a short period of time, we have identified benefit with 2 novel targeted agents for lymphoma, whereas most new approaches with cytotoxic therapy have been less successful. With standard cytotoxic treatment failing in approximately 30% of this pediatric population, we are now looking at integrating these 2 targeted agents with chemotherapy to see if they can improve outcome for children with ALCL.

H&O How do drug shortages impact treatment of children?

PA Drug shortages vary in their severity and impact. In the United States, many of the drugs that are lifesaving for children come from a sole supplier. If there is a problem with that supply, the entire country can experience a

shortage. The most recent example occurred with *Erwinia chrysanthemi* asparaginase (Erwinaze, Jazz Pharmaceuticals), which is used for children who develop allergies to frontline PEGylated *Escherichia coli* asparaginase, a critical component of ALL therapy. For a period of time, supplies of *Erwinia asparaginase* dwindled, and patients may have had to go without it. Drug shortages are an ongoing problem. The FDA's Office of Drug Shortages has been very supportive, but this problem cannot be solved solely by the FDA.

H&O You are chair of the Children's Oncology Group (COG). What type of work does it do?

PA The COG is the primary, largest organization that conducts clinical-translational research in children with cancer. It consists of more than 220 sites throughout the United States and Canada, as well as some sites in Australia and New Zealand. The portfolio generally includes more than 50 open clinical trials. Virtually all phase 3 studies in North America are conducted by the COG or in collaboration with the COG. Many phase 2 trials, and a significant number of phase 1 studies, are also conducted by the COG.

In the United States, we estimate that more than 90% of children are cared for at one of our member sites. Upwards of 60% of newly diagnosed children participate in research studies, depending on their age and the trial protocol. We are fortunate that so many children and their families are committed to working alongside the pediatric oncology community for clinical research.

The COG is predominantly funded by the NCI and philanthropic support. Like other groups in the NCI, the COG has been subject to significant cuts in funding or flat funding for many years now.

H&O What are some other areas of research being explored by the NCI?

PA To provide direction for the Cancer Moonshot, cancer experts from across the country were assembled by

the NCI into a Blue Ribbon Panel. I was privileged to co-lead the pediatric working group for the Blue Ribbon Panel. We put forward several recommendations for pediatric cancer research that have the potential for significant impact. One of the recommendations is for a comprehensive program to better understand fusion oncoproteins. Another major recommendation concerns immunotherapy. The targets for immunotherapy in childhood cancers differ from those in adults, and thus distinct efforts to develop effective immunotherapy for children with cancer are needed.

Disclosure

Dr Adamson has no real or apparent conflicts of interest to report.

Suggested Readings

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