Precision Medicine for Pediatric Cancers Lags Behind That for Adult Cancers

Citing hurdles in clinical trial recruitment and drug development, researchers are exploring ways to close gaps

Although scientists have made great strides in applying breakthroughs in precision medicine to many adult cancers, the same cannot be said of pediatric diseases. However, researchers, advocates, and lawmakers are hoping to bridge the divide, largely by identifying more opportunities to include children, adolescents, and young adults in precision oncology clinical trials.

Exactly why pediatric precision oncology has experienced fewer research gains is a varied and complicated issue, according to experts. Nonetheless, Katherine Janeway, MD, a senior physician and director of clinical genomics at the Dana-Farber Cancer Institute and Children's Hospital in Boston, Massachusetts, points to several important drivers of the disparity. She co-authored an article in a March 2019 special edition of *Science* that outlined problems and possibilities in the field.[1]

First, although pediatric cancers remain the second leading cause of death in children aged 1 to 14 years, they are considered rare and tend not to receive as much attention and research funding as more common cancers. Approximately 11,060 children in the United States are projected to have been diagnosed with the disease in 2019,[2] which accounts for less than 1% of all cancers, according to the American Cancer Society. "It is a greater challenge to fully characterize rare diseases because you need to sequence a large number of each rare pediatric cancer to fully characterize the genome," Dr. Janeway says.

Second, she says, to validate the use of a specific drug against a certain cancer type with a particular biomarker characteristic, researchers must develop models of those subtypes. In turn, the models must get into the hands of the pharmaceutical industry, which then would take the lead in drug development. "We haven't had as many validated preclinical models, which are primarily cell lines and mouse models, in the right place at the right time," she says.

Furthermore, pharmaceutical interest has long been unreliable, with the industry viewing drug development for pediatric cancers as unprofitable. Indeed, although approximately 900 drugs are in the pipeline for adult cancers, only a few are in development for children, according to Kids v Cancer, a nonprofit advocacy organization.

Lastly, some of the more common genomic events in pediatric cancers are harder to target. According to Dr. Janeway, many pediatric cancers are characterized by canonical transcription factor gene fusions, which can be challenging to treat with current precision therapies.

Despite these barriers, Dr. Janeway and others have seen progress on a variety of fronts. One is the regulatory landscape. To spur improvements in drug development, Congress passed the Research to Accelerate Cures and Equity for Children (RACE) Act in 2017; it goes into effect this year. Although not a new law, the RACE Act updates the Pediatric Research Equity Act (PREA), which was approved in 2003. PREA gives the US Food and Drug Administration (FDA) the authority to require that pharmaceutical companies conduct pediatric studies for drugs already under review for adult indications.

According to Kids v Cancer, PREA has not been applied to cancer because children's cancers often originate in different parts of the body from adult cancers. What is more, PREA requirements were typically waived for cancer drugs that had been designated as orphan drugs by the FDA. (The FDA Orphan Drug Designation program provides orphan status to drugs and biologics that are intended for the treatment, diagnosis, or prevention of rare diseases affecting fewer than 200,000 people in the US.)

The RACE Act ensures that cancer drugs with orphan disease designations will no longer be exempt. The ultimate goal, of course, is to increase pediatric oncologists' access to novel therapies, with the potential of helping their patients live longer. Moreover, the act gives the FDA the authority to require that any new cancer drug be studied in pediatric cancers for which the molecular target of the drug is relevant. That

requirement is helpful because some adult and pediatric cancer treatments do share molecular targets, such as an *ALK* inhibitor, which treats both adults with lung cancer as well as children with neuroblastoma.

"Since adult cancers are more frequent than pediatric cancer, finding common molecular targets will greatly enhance our ability to access new targeted drugs and identify distinct targets only seen in pediatric cancers," says Victor Santana, MD, senior vice president of clinical trials administration at St. Jude Children's Research Hospital in Memphis, Tennessee. "The RACE Act may help by ensuring that when there is a commonality, these target-specific drugs will also be studied in children."

Expanding the Age of Eligibility

In another effort to ensure that the latest drug discoveries are made available to as many younger patients as possible, the FDA issued a draft guidance in March 2019 stating that pharmaceutical companies can enroll adolescents in adult clinical trials after they have obtained pharmacokinetic and toxicity data and if those patients have recurrent cancers or no other treatment option. According to Dr. Janeway, the impact of the draft guidance is visible, as "it already has become fairly standard to see clinical trials expanding their eligibility to age 12 and above." Indeed, early-phase trials that determine acceptable doses and side effects have indicated that both are similar to those of adults, she notes.

Although acknowledging that cancers in younger populations can be highly different from those in adults, the FDA notes that several types, including soft tissue or bone cancers, central nervous system tumors, leukemias, lymphomas, and melanomas, are similar enough that sponsors should evaluate ways to enroll adolescents onto such trials. The *Science* authors emphasize that academic partners in these trials will need to develop strategies for simultaneously enrolling participants from both pediatric and medical oncology clinics, given that care and research for these patients are separate in many institutions.

The field of immuno-oncology already has made a significant impact in patients with pediatric leukemia, says Dr. Santana. The FDA has approved chimeric antigen receptor (CAR) T-cell treatment against antigens expressed on leukemic cells, and a new class of treatment called BiTE (a bispecific T-cell engager) enables a patient's T cells to recognize malignant B cells in pediatric lymphoid leukemia. Still another example

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is the development of humanized antibodies against GD2, which is an antigen expressed in neuroblastoma cells. When the antibody is used in conjunction with chemotherapy, it has been found to improve survival in children with metastatic neuroblastoma. Researchers at St. Jude Children's Research Hospital are investigating these and other types of targeted therapies, including those that target brain tumor mutations. One example of the latter is the SJELIOT trial, which is assessing a molecularly targeted CHL1/2 inhibitor in combination with cyclophosphamide or gemcitabine for children and adolescents with a specific type of refractory or recurrent medulloblastoma.

According to Dr. Janeway, one of the main goals she and her colleagues had when writing the *Science* article was to highlight the most difficult-to-target genomic features of pediatric cancers in the hopes of attracting interest from pharmaceutical researchers. Drugs currently being studied against these targets are still in early-phase clinical trials, but she says some appear promising, including a class of drugs known as EZH2 inhibitors. These target abnormalities in rhabdoid tumors and epithelioid sarcomas. Other potential agents currently undergoing phase 1 trials target the oncogenic transcription factor, EWSR1-FLI1, in Ewing sarcoma.

"One of the things that is going to help is data sharing, which is getting a lot of attention right now in childhood cancer," Dr. Janeway says. "The NCI's [National Cancer Institute's] Childhood Cancer Data Initiative is focusing on doing that. At the same time, there needs to be continued sequencing of pediatric cancers, both in the clinical and research spaces."

References

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Psychological Stress Is Associated With a Higher Risk of Cervical Cancer Mortality

Women with cervical cancer who experienced a stress-related disorder or a stressful life event were more likely to die of the disease than those who had not reported stress, according to a study published in *Cancer Research*.[1]

Previous experimental and epidemiological studies have indicated that stress-related psychiatric disorders could affect disease progression in numerous cancer types. To explore this link further, investigators from the Karolinska Institute in Stockholm, Sweden, led by postdoctoral researcher Donghao Lu, MD, PhD, analyzed records from 4,245 patients who were diagnosed with cervical cancer in Sweden between January 1, 2002, and December 31, 2011. Data from the Swedish Patient Registrar were used to identify patients who had been diagnosed with one of the following: stress reaction and adjustment