Seeing a Promising Future For Progress Against Childhood Cancer

For Childhood Cancer Awareness Month, the National Cancer Institute's Director Dr. Ned Sharpless reflects on childhood cancer progress.

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In 1982, Dr. Mariano Barbacid, a researcher working at NCI, and his colleagues identified a gene, called NTRK, that could transform healthy cells into cancer cells. Four years later, some of the same researchers reported that their initial discovery was only partially correct. The gene they had discovered refashioned healthy cells into cancerous cells only when it was joined to another gene, a molecular event known as a gene fusion.

Decades of further study defined how NTRK works under normal circumstances and how its improper activation causes cancer. These discoveries formed the basis for the development of drugs called NTRK inhibitors that were later shown to be highly effective against cancers that are fueled by gene fusions that involve NTRK. Given their impressive activity in clinical trials, NTRK inhibitors were recently approved by the FDA for the treatment of cancers with NTRK fusions, which occur in children and adults.

The success of NTRK inhibitors is not only a testament to the importance of basic science but also an excellent example of recent progress that's been made for children with cancer. There are, I'm happy to say, many other examples.

Among the most well-known is the development of CAR T-cell therapies that can cure some children with very advanced forms of leukemia. Perhaps less familiar are the Children's Oncology Group (COG)-led clinical trials that have pioneered ways of making often curative treatments for some children with cancer far safer, sparing kids from some short- and long-term treatment side effects, including hearing loss and infertility.

In recognition of Childhood Cancer Awareness Month, I want to reflect on the progress that's been made against cancers that largely affect children.

For example, acute lymphoblastic leukemia (ALL) was uniformly lethal in children prior to the 1950s, but now, with modern approaches to this disease, more than 90% of children with ALL are cured. Overall, the mortality rate from all types of cancer among children and teens has dropped by more than 50% since 1980, and the substantial majority of kids with cancer today are cured of their disease.

But any discussion of progress also requires that we recognize where advancement has lagged.

For some types of childhood cancer, such as soft tissue and central nervous system cancers, long-term survival is still poor and treatment advances have been limited. Moreover, children cured of their cancer may face a lifetime of health problems caused by their disease and its treatment, including aggressive surgeries, radiation, and chemotherapy.

These lingering disappointments have strengthened the resolve and commitment of the research community to discover innovative ways to cure as many children with cancer as possible—and to do so in a manner that causes the least long-term side effects for survivors. In my view, we are taking the necessary steps to achieve that end.

Data Leading the Way

I'm particularly excited about the radical transformation in the collection of data on children with cancer and the expanded ability to share it across the research community.

Data may not seem like the most compelling topic. But with efforts being conducted as part of the Childhood Cancer Data Initiative (CCDI), we are laying the groundwork for learning from every child with cancer. CCDI, I should note, builds on other NCI activities supported by the STAR Act, federal legislation enacted in 2018 to accelerate progress against childhood cancers.

I've met with researchers from across the country who specialize in pediatric cancer, and I can confirm that they are excited about this new world of data collection and sharing.

Take, for example, one CCDI-related program called the National Childhood Cancer Registry. This registry is collecting and linking data on diagnosis, outcomes, treatments, and long-term side effects for nearly every child with cancer in the United States.

Another CCDI effort, a national Molecular Characterization Protocol, will facilitate the collection of tumor tissue from children who have cancers for which such tissue for research is lacking or inadequate. A priority will be placed on cancers for which existing treatments are limited or ineffective.

As part of this protocol, researchers will perform in-depth molecular characterization (e.g., whole-genome sequencing and RNA sequencing) of this tumor tissue. Those data can be shared with patients' oncologists to help enroll kids in precision medicine clinical trials and help guide their care and will also be available to pediatric cancer researchers through tools like the Genomic Data Commons.

Having access to such comprehensive molecular information that is linked to each patient's clinical data (e.g., treatments received, stage of cancer) will provide unprecedented insights into the drivers of childhood cancers and how they become resistant to treatment, as well as factors that influence the risk of treatment-related side effects. It can also help identify potentially powerful combinations of targeted therapies, which I believe will be critical to improving outcomes.

These data and resources also will help provide answers to questions that can't necessarily be addressed through clinical trials. Collecting comprehensive data from as many children as possible will give researchers a more thorough understanding of how well treatments work in "real world" populations. These data will also make it easier for researchers to monitor the health of survivors

of childhood cancer throughout their lives, providing further insights into the impact of cancer and its treatments.

Advancing Precision Medicine in Childhood Cancer

A problem in clinical oncology is knowing the best treatment to give a patient. There are many medicines to treat cancer, and they can be combined with surgery and radiation in various complex regimens. But given all these possible choices for therapy, it is often not clear what is the best treatment for a given patient.

Currently, pediatric oncologists usually make treatment choices for their patients based on the best available evidence from historical clinical trials. For the child, and their family, this means starting therapy and waiting to see if those choices were effective.

For many children, that may mean going on treatment for a few months, and then having imaging scans done to see if the cancer is regressing. But it's also a few months where the cancer might be getting worse, a few months of potential side effects, a few months of costs associated with treatment, and a few months of anxiety and distress for the child and their loved ones.

It would be far better to be able, at the time of diagnosis, to know which treatment approach is most likely to work. Determining the best treatment would rely not just on findings from previous trials but also specific information about the patient and their cancer. We don't collect this molecular information uniformly today—and even when we do collect it, we don't know how to interpret it completely to make these therapeutic decisions, particularly in children.

That's where efforts like those being developed under CCDI come into play. And it's also why precision medicine trials like the NCI–COG Pediatric MATCH trial (and its companion trial in adults, NCI-MATCH) are so important. Trials like Pediatric MATCH—and similar studies being conducted in EuropeExit Disclaimer and AustraliaExit Disclaimer—are teaching us how to use DNA, RNA, and protein data to identify the most effective treatments for each individual child's cancer.

Although time will tell, I'm hopeful that these studies will help point the way to important answers about more effectively treating cancer, identifying new targeted therapies and treatment combinations that are highly effective in children.

Advancing Immunotherapy for Children with Cancer

Over the past decade, immunotherapy has offered a true paradigm shift in how we think about treating cancer. Although its impact has been greatest in adults, immunotherapy is also changing how we treat some children with cancer.

Several CAR T-cell therapies, for example, are approved to treat children and adolescents with leukemia and have led to cures for a modest proportion of children with very advanced disease.

NCI continues to be a leader in advancing CAR T-cell therapies for childhood cancer, leading early-phase clinical trials of new types of CAR T cells. We've also launched an initiative to manufacture CAR T-cell therapies to be used in clinical trials being run at multiple centers across the country. This initiative is already expanding the number of children who can participate in trials of CAR T-cell therapies and offers the hope of moving these new therapies into everyday patient care much

more rapidly.

NCI also played a crucial part in advancing dinutuximab (Unituxin) to become a standard immune-based treatment for children with neuroblastoma. Dinutuximab's molecular target, a protein on cancer cells called GD2, is also the target of a promising CAR T-cell therapy. NCI is supporting an early-phase trial of this GD2 CAR T-cell therapy for children with one of several types of solid tumor, including osteosarcoma, neuroblastoma, and melanoma. Another trial at Stanford University has already launched testing GD2 CAR T cells in children with a uniformly fatal form of brain cancer called DIPG.

And thanks to initiatives like the Cancer Moonshot[SM]-supported Pediatric Immunotherapy Discovery and Development Network, a path is quickly being blazed to expand immune-based treatments in children with cancer. That includes research to improve upon CAR T-cell therapies, support the development of other cellular therapies and other forms of immunotherapy, and expand their use to more types of childhood cancer.

The Imperative of Addressing Childhood Cancer Disparities

We should be encouraged by the progress that's been made against childhood cancer, whether it's improved survival outcomes using standard treatments like chemotherapy and radiation or novel therapies like bispecific antibodies.

But let me be clear: We must ensure that all children and adolescents with cancer will benefit equally from this progress.

Indeed, studies have documented disturbing racial/ethnic disparities in cancer incidence and survival rates. And, unfortunately, our youngest are not shielded from this harsh reality. Even for cancers that are highly curable, studies have found that Black and Hispanic children do worseExit Disclaimer than their White counterparts.

Numerous systemic and societal factors contribute to health disparities. That includes everything from underserved populations receiving less effective care, a lack of health care facilities in lower-income and rural areas, and the many problems that come with lower socioeconomic status, such as reduced educational attainment, increased exposure to environmental pollutants, and a higher likelihood of other health problems.

Given the structural and systemic nature of the causes of health disparities, directly resolving these societal problems is beyond the scope of a research agency like NCI.

Even so, NCI can and does support research that provides an evidence base for informing policy and clinical practice, advancing the science of disparities. Such studies include those that are allowing us to better understand the relative contribution of the factors that cause disparities, as well as those testing ways to help remedy disparities at the institutional and community level.

It also means supporting research to identify biological factors that contribute to disparities. For example, Hispanic/Latino children are not only at a higher risk than White children of being diagnosed with B-ALL, the most common form of leukemia, but even after accounting for factors like access to care and family income, these children have a higher risk of dying from the disease.

A recently published NCI-funded study identified a potential culprit that might contribute to this disparity: specific genetic changes, including a fusion gene, that are far more common in Hispanic/Latino children with B-ALLExit Disclaimer.

Why these changes are more common in Hispanic/Latino children with B-ALL is unclear, and so is exactly how they contribute to a worse prognosis. But these kinds of studies can identify children for whom standard treatments may not be sufficient and point the way to new, more effective treatment approaches for their specific cancers.

A More Hopeful Future for Kids

This is just a sampling of the research that I believe will, in coming years, expand the number of children with cancer who are cured, including those children with cancers that currently have few effective treatments.

Advances will come from many spaces, whether it's the Cancer Moonshot-supported Fusion Oncoproteins in Childhood Cancer Consortium, studies of survivors of childhood cancer, or the many labs across the country working on new forms of cellular therapies.

And progress will come from basic science studies that, like the one Dr. Barbacid led all those years ago, were not specifically intended to address childhood cancer but, in the end, will save children's lives.

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