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Democracy Dies in Darkness

To save children with cancer, doctors turn to new weapons

Pushed by parent activists and buoyed by new funding, scientists explore novel strategies to treat deadly pediatric cancers

By Marlene Cimons
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When Michelle Monje was a medical student 20 years ago, she saw her first case of diffuse intrinsic pontine glioma, a childhood brain cancer that is almost always fatal within a year. Monje decided to study the disease further — "I just couldn't turn away" — but several senior faculty members tried to talk her out of it.

They "were concerned there was little interest because the disease was so rare and that I would struggle to accomplish anything," she recalls.

Such was the state of pediatric cancer research at the time. But the field has undergone a remarkable shift in the past decade.

Today, armed with data from technological advances and pressed by parent advocates, scientists are exploring novel strategies to treat childhood cancers. These include manipulating immune system cells, proteins and other molecules to design targeted therapies they believe will be more precise and less toxic than conventional chemotherapy.

Although cancer is rare in children, it still is their leading cause of death from disease. Last year, the National Cancer Institute (NCI) projected 10,500 new cases in children from birth to age 14 in 2021, with 1,190 deaths, although some experts think the number probably is higher. The most common types of childhood cancers include leukemias, brain and other central nervous system (CNS) tumors, and lymphomas, according to NCI.

Catherine Bollard, director of the Center for Cancer and Immunology Research at Children's National Hospital Research Institute in D.C., acknowledges that there are more adult cancer patients, the long-standing reason that drug companies have favored drug research in them. But curing children makes a long-lasting impact.

"Kids who survive will be productive citizens for a longer time than an adult you are trying to give an extra five years to," she says.

'A long way to go'

Pediatric oncologists applaud the recent progress, adding that the pace needs to continue.

"These changes in recent years have prompted approaches that are beginning to make a real impact on improving the care and outcome of children with diseases thought incurable 10 years ago," says Paul Sondel, the Reed and Carolee Walker professor of pediatric oncology at the University of Wisconsin School of Medicine and Public Health and a pediatric oncologist for more than 40 years. "Nevertheless, while we are seeing new progress, we know there is still a long way to go to be able to cure all children with cancer."

Dinah Singer, senior investigator in the National Cancer Institute's Experimental Immunology Branch and the head of NCI's molecular regulation section and deputy director for scientific strategy and development, agrees, but she insists scientists' commitment to children never wavered, only that the previous challenges had been formidable.

Today, scientists know much more about kids' cancers than they did before.

“We’ve always had a long-standing continuing interest in pediatric cancer,” she says. “What’s changed is our understanding of how fundamentally different childhood cancers are from adult cancers, which has opened new [research] opportunities.”

‘Children are wired differently’

Pediatric cancers are unique and cannot be treated like adult cancers, experts say.

“Children are wired differently,” says Crystal Mackall, the Ernest and Amelia Gallo family professor and professor of pediatrics and internal medicine at Stanford University and former chief of NCI’s Pediatric Oncology Branch. “Adults acquire a lot of cell mutations, step-by-step,” which is why most people who get cancer are older. “Children’s cancers are more like a switch — boom — and turning off that switch is difficult because their cancers aren’t molecularly the same.”

Bollard agrees. “There has been this assumption that we can just take drugs that work in adult cancers, and they will work in kids,” she says. “That is not correct. We can’t rely on trickle-down therapeutic approaches.”

While chemotherapy has been effective against childhood blood cancers, such as acute lymphocytic leukemia (ALL) — the most common childhood leukemia — it is has been less successful against solid tumors. Moreover, children receiving chemo and radiation risk serious health effects later, including new cancers and heart and lung problems, among others.

“We don’t worry about long-term side effects in a 70- or 80-year-old, but we have to worry about them in children,” says Douglas Hawkins, professor of hematology-oncology at Seattle Children’s Hospital and chair of the Children’s Oncology Group, an NCI-funded consortium of more than 200 hospitals treating and studying children with cancer. “If we cure cancer in a 3-year-old, it’s not to prolong their lives for a few months but for life. The gains to society are enormous.”

NCI spending for pediatric cancer research rose from 5.57 percent of its budget in fiscal 2016 to 8.77 percent in fiscal 2021, according to the institute. Also, the National Institutes of Health — of which NCI is a part — invested about $664 million on childhood cancer research in fiscal 2021, an increase of $85 million over fiscal 2020, according to NCI. NCI's overall budget for fiscal 2021 was nearly $6.4 billion.

Scientists welcome the boost but say they still could use more. "This is a helpful increase, but still not sufficient to make the impact that childhood cancer really needs, especially given the years of life that potentially could be saved," Sondel says.

Cell-based immunotherapy

Monje, now a pediatric neuro-oncology researcher and physician at Stanford University, ignored that long-ago advice and stuck to her plan.

She and Mackall are developing a cell-based immunotherapy known as CAR (chimeric antigen receptor) T cells to treat the brain tumor that so frustrated her as a medical student. Early results are encouraging.

The technique involves removing immune T cells from the patient, engineering them in the lab to recognize cell markers abundant on tumors, then returning them to the patient. The altered cells include a protein — the CAR — that doesn't occur in nature. The CAR protein binds to the tumor and stimulates the engineered T cells into multiplying, then attacking and killing cancer cells.

Although not yet curative, Monje and Mackall are excited by the behavior of the cells and plan to further fine-tune them. "It's still early and I don't want to overstate it, but given that this is a disease where nothing has worked, it's unbelievable," Mackall says.

"These CAR T cells are so specific, they just go into the tumors," Monje says. "We see a response within weeks of their getting so much better symptomatically. We've seen kids go from wheelchairs to walking in two weeks. Although the cancer came back, three of the first four kids we published on had great a therapeutic response."

Giving a second dose brought improvements, and now the team administers monthly infusions, hoping they will provide a more durable response, Monje says. They plan further modifications to the cells and will test them in the lab before giving them to patients.

As with most scientific progress, steps are incremental, she says. “This process of iteration, of bench-to-bedside, then bedside-to-bench, again and again, is how we will eventually cure diffuse intrinsic pontine glioma,” she says.

CAR T products have been approved to treat certain blood cancers in adults and children, but not for solid tumors. These are more resistant to the therapy, probably because malignant cells in blood cancers are more accessible to roving CAR T cells, cancer experts say.

Bollard, with Martin Pule of UCL Cancer Institute of University College London, recently received about $24 million from the Cancer Grand Challenges program, funded by NCI, Cancer Research UK and the Mark Foundation for Cancer Research, to study hard-to-treat childhood solid tumors. They too are investigating the use of CAR T cells.

They are manipulating CAR T cells to make a protein that can block transforming growth factor beta (TGF-Beta), “a nasty cytokine that has devastating effects on T cells’ ability to grow and kill tumors,” Bollard explains. (Cytokines are small proteins that affect the activity of immune system cells.) “Most human cancers use TGF-Beta to evade the immune system,” Bollard says, adding the idea is to “power up” CAR T to thwart this cytokine.

“We want CAR T to become the standard of care within a decade for children with these solid tumors,” she says.

Targeted therapies

Targeted therapies such as CAR T represent “the next revolution” in treating childhood cancers, says Andrew Kung, a pediatric oncologist who chairs the pediatrics department at Memorial Sloan Kettering Cancer Center in New York. “We are very excited about their potential pediatric applications,” he says.

He cites antibody-based therapies as additional promising approaches, among them antibody drug conjugates and “bi-specific” antibodies.

Conjugates are monoclonal antibodies — laboratory-made proteins that latch on to certain targets, such as antigens (foreign substances in the body) on cancer cells — that are chemically linked to drugs. The antibodies release the drugs, which kill cancer cells without harming other cells. “Bi-specific” antibodies contain two arms, one that binds to cancer cells, the other to T cells, and deploys them to fight the cancer.

Experts point out that technological advances underscoring these therapeutic advances don’t fully explain the current resurgence. They laud the work of parent advocacy groups; the willingness of hospitals and academic institutions to collaborate; data sharing, such as via the Childhood Cancer Data Initiative; legislation such as the Childhood Cancer Survivorship, Treatment, Access and Research (STAR) Act, which authorizes $30 million annually for pediatric cancer research; and a regulatory environment that has become more child-friendly.

The Children’s Oncology Group, for example, an NCI-funded global pediatric clinical trials consortium with more 10,000 experts in the field, seeks to eventually develop standards of care for pediatric cancer.

“Even the biggest institutions see only a handful of pediatric cancer cases, so the best way to study them is to band together,” says Hawkins, its chair, who says the consortium is sponsoring at least 100 clinical trials. “You can study breast cancer at one institution, but if you want to study pediatric cancer, you have to work together.”

Parents’ powerful voices

Also, new inducements and rules have prompted the pharmaceutical industry to include more children in their drug research. The Race for Children Act, for example, requires drug companies testing a targeted cancer drug for adults to test it in children if the drug’s same molecular targets are found in pediatric cancers — even if the kids’ cancer is different. “This is huge,” Hawkins says. “It’s a game changer.”

The Creating Hope Act establishes a system that awards vouchers to companies that develop drugs for rare pediatric diseases, entitling them to a speedier review for a future drug for any disease. Companies can use them for their own drugs or sell them to another company. Either way, it enhances their profits.

Finally, experts praise those parents who've lost children to cancer and organizations they started — for example, the EVAN Foundation, Alice's Arc, the Smashing Walnuts and Kids V Cancer — for provoking strong bipartisan support for many of their initiatives.

"They keep reminding us of the devastation having a child with cancer can have," Singer says.

"A parent of a child with cancer is probably the most powerful lobbying voice there is," Bollard says. "It's true that adult cancers occur in a much larger number of people. But if it's your child — or my child — with cancer, that's the only patient who matters."