

A framed photo of a young girl with wispy blond hair and chubby cheeks rests on a shelf in the office of Howard Katzenstein, M.D. She's squinting into the sun, and she has a slight smile — not quite joyful, but happy enough. She is only 2 years old in the picture, but already Bridget has shared a life-and-death battle with Dr. Katzenstein. Together, they fought a stealthy opponent, a tumor that spread from her hip bone to her lungs and spine before it was even detected.

No Stone Unturned

Experimental cancer therapies improve chances of survival



Bridget is 5 years old now. It's a miracle she's alive. **Conventional treatment gave her less than a 10 percent chance of survival, but Bridget has done remarkably well with the experimental therapy she received from Dr. Katzenstein and his colleagues at Children's Healthcare of Atlanta.** She shows no signs of cancer, although Dr. Katzenstein is reluctant to say she's "cured." He will continue to monitor her condition hoping to reach the five-year, cancer-free milestone.

The photo serves as a reminder why he engages in a constant search for a better cancer treatment – the dire circumstances of his patients, their courage and the hope for the future. Pediatric cancer patients benefit from the groundbreaking work performed at cancer centers like the one at Children's, where basic research moves quickly into clinical trials and novel treatments. They also take a new approach to existing therapies, using drugs in different combinations or doses to improve their effectiveness or reduce side effects.

"Experimental therapy with novel drugs is really for families who are not ready to give up, who want to make sure they've left no stone unturned," said Dr. Katzenstein, Director of Clinical Research and Experimental Therapies at the Aflac Cancer Center and Blood Disorders Service at Children's Healthcare of Atlanta.

Great strides have been made in pediatric cancer treatment in the last 35 years, thanks to the focus on experimental therapy. Of the 12,000 to 15,000 new pediatric cancers diagnosed each year, about 75 percent are cured. The history of leukemia treatment is an inspiring example of this success. In 1960, the cure rate was only 14 percent. After years of clinical trials with new combinations of chemotherapeutic agents, radiation, and blood and marrow transplants, the cure rate has risen to about 80 percent.

Yet there's much more work to be done. About 60 percent of pediatric patients participate in clinical trials. That number would be even higher if more clinical trials were available, Dr. Katzenstein said. Some have cancers that afflict only a handful of children each year, a group too small to attract the



attention of many pharmaceutical companies. Pediatric cancer centers conduct basic research to search for novel therapies. In fact, within the next year, the Aflac Cancer Center plans to begin clinical trials on a new agent that targets a unique intercept point in cancer cells.

"What we're doing is a paradigm shift in the evolution of drugs for cancer," said Donald L. Durden, M.D., Ph.D., Scientific Director of Basic and Translational Research at the Aflac Cancer Center. "This will be the first example of a drug to hit that pathway in the cancer cells."

Beyond the Protocol

By participating in clinical trials, pediatric cancer patients shape the future of medicine. But the trials aren't just for the



researchers. It's important for cancer patients to have access to the most current approaches to treatment and, if necessary, experimental therapy.

"Pediatric oncologists work together nationally to devise a standard protocol for newly diagnosed patients – how to dose, how often to do scans, how often to go to the doctor," Dr. Katzenstein said. In those cases, the difference between cancer centers lies in the experience of their physicians and whether they're involved in state-of-the-art research, he said.

Comparing Centers

When pediatricians refer their patients to an oncology group, they should consider the volume of patients treated by the center, the scope of clinical trials available there, and the expertise of their physicians and research scientists, advises Dr. Katzenstein.

Last year, the Aflac Cancer Center saw more than 300 new oncology patients. Some of those had cancers rarely seen outside of the top pediatric cancer centers. Others were the most common cancers that afflict kids. But early in their treatment, it's impossible to know whether the cancer will follow a predictable pattern or whether it will take a difficult and deadly course.

Take the case of Carter, a 7-year-old with Ewing's sarcoma, a bone tumor most often found in children between the ages of 10 and 20. Carter received 14 cycles of the standard five-drug treatment and responded well. It seemed he would be one of the lucky ones. But then the cancer recurred, and it didn't respond to second-line therapy.

Unfortunately, Carter didn't qualify for a Phase I trial because of lingering side effects from his previous

chemotherapy. He died. Carter was a boy with a wonderful spirit and sense of determination. He emptied his piggy bank and donated his coins to the Aflac Cancer Center's experimental therapy program. His death was a reminder of the urgent need to continue searching for more effective treatments. "It keeps you humble," said Dr. Katzenstein.

What happens when the frontline treatment doesn't work? What are the options? Those are questions that the parents of pediatric cancer patients should ask when they meet with an oncologist. They also should ask about the cancer center's track record. How many pediatric blood and marrow

transplants are performed at the center? What is the 100-day mortality rate after bone marrow transplant? What is the survival rate at the center for the child's cancer type? How does it compare to the national average?

While there are no guarantees, the "average" track record will apply to any particular case, a cancer center's outcomes reveal much about their approach to therapy and their experience with a variety of cancers. Which center a patient's family chooses will shape the course of their treatment and their possibilities.

In comparison to the Surveillance, Epidemiology and End Results (SEER) program, the Aflac Cancer Center's patients exceed the national outcome standards. A program of the National Cancer Institute, SEER is the authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26 percent of the U.S. population.

The Aflac Cancer Center also has an excellent track record with blood and marrow transplants. Physicians at the center performed 73 transplants last year. In 2005, the day 100 mortality rate for both autologous and allogeneic bone marrow transplants was 0 percent compared with a national mortality rate of 10 percent for autologous and a national mortality benchmark of 20 percent for allogeneic.

Taking the Phase I Risk

Phase I trials represent the cutting edge of experimental cancer treatment. These trials are for patients like Bridget, who otherwise have little hope for survival. The trials test new drugs that show promise in animal studies, but for which the most effective and safest dosing isn't yet clear.

Dr. Katzenstein is committed to giving parents as much information as possible about what they can expect from clinical trials. He has launched an ethics study to look at parents' opinions about experimental cancer therapies.

"People affected by those diseases want quicker access to drugs and are willing to take more risks," he said. "As physicians, it's important for us to explain the risks and the benefits to the patient."

The Aflac Cancer Center is a part of the Children's Oncology Group (COG), an international consortium of more than 200 medical institutions that is funded by the National Cancer Institute. The COG is one of the largest clinical trials organizations in the world. The Aflac Cancer Center also participates in a number of other collaborative studies and trials including the Pediatric Oncology Experimental Therapeutics Investigators Consortium (POETIC) and New Approaches to Neuroblastoma Therapy (NANT).

Dr. Katzenstein and his colleagues currently manage about 13 Phase I trials and another 19 Phase II trials. The Aflac Cancer Center also treats adolescents and young adults (age 15 to 21), who can benefit from the pediatric protocols and access to clinical trials. Due to their age, adolescents and young adults are often treated at adult hospitals where they don't have access to pediatric clinical trials. Outcome data has shown that many adolescents and young adults realize better outcomes from being on pediatric clinical trials versus adult clinical trials.

"We do what we can to get the patient cured. That's the perfect result," said Dr. Durden. "If they relapse, we want them to get the most current experimental therapy."

Discovering Hope

For patients, clinical trials represent hope. The cancer of Bridget, the girl whose picture is on Dr. Katzenstein's desk, was diagnosed in 2002 when her parents discovered a lump on her hip. A CT scan and MRI revealed the cancer had already spread. Dr. Katzenstein and his colleagues designed a novel protocol of radiation and a four-drug, high-dose chemotherapy, which was preceded by an autologous blood and marrow transplant.

The radiation caused an inflammation of her intestines as well as some kidney problems, which have largely resolved. She was fortunate to avoid other potential effects, such as hearing loss or developmental delays.

But intensive treatment isn't for everyone. Dr. Katzenstein noted the case of an 18-year-old girl who had a tumor that was incurable. The tumor didn't respond to chemotherapy and radiation treatments. The girl could have been a candidate for a Phase I trial, but she declined. At best, the treatment would have given her a short extension of her life, not a cure. "She said, 'I've gotten so sick with my chemotherapy. I don't want any more. I don't want to be that sick,'" recalled Dr. Katzenstein.



Dr. Katzenstein's dream is to be able to offer a cancer treatment that will have fewer toxic effects and better outcomes, a treatment that will give realistic hope to more of his patients. With each new clinical trial, he feels a step closer to that day. 📧

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A New Plan of Attack: Targeting a New Receptor

The newest cancer drugs are like biological missiles. They are on a search-and-destroy mission as they target a spot on the cancer cell. A more specific honing device leads to a better "hit" rate.

That is a simplified explanation of the work of Donald L. Durden, M.D., Ph.D., Scientific Director of Basic and Translational Research at the Aflac Cancer Center and Blood Disorders Service at Children's Healthcare of Atlanta.

The newer cancer drugs on the market today target receptors in the cell wall. There are 10,000 receptors in any given cell, and the cell may continue to function despite an attack by the anti-cancer drug on a single receptor. Dr. Durden was able to identify a "bottleneck" point within the cancer cell that serves as a kind of "master control switch" for cancer cell survival. He then identified an inhibitor that will target that intercept point.

"We've made this like a smart bomb," said Dr. Durden, who holds or has applied for 10 patents related to his cancer research. "It's like a laser-guided

missile." By inhibiting all PI3-kinases in the cancer cell, it can shut down 80 percent of the survival capacity of the cell — compared with just 0.1 percent for the receptor targets of other cancer drugs. It also enhances the destructive capability of chemotherapy and radiation. This experimental drug will likely be used in conjunction with radiation therapy and other chemotherapeutic agents, said Dr. Durden.

In animal models, the drug's impact varies based on the type of cancer. In studies, brain tumors disappeared after treatment, while rhabdomyosarcomas (muscle tumors) shrank

significantly. Dr. Durden expects Phase I trials to begin within a year in adults with brain tumors, prostate and breast cancer. Within two years, he hopes to be able to move the drug into clinical trials with pediatric patients.

This drug development is possible because the marriage between research and clinical practice at the Aflac Cancer Center. "This is a mission for me to get this drug into pediatrics," said Dr. Durden, a pediatrician who still sees oncology patients. "At every point along the way, we asked, 'How can we translate this from the bench to the bedside?'"