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In this issue:

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Director's Update

Pediatric Oncology Partnerships Are Models for Success

In this special issue of the *Bulletin*, we pay tribute to pediatric oncology, focusing on the wide-reaching partnerships that have led to exemplary progress in treating children with cancer. As you will see, these partnerships have markedly reduced pediatric cancer mortality and will most certainly hasten our progress against other cancers, such as osteosarcoma and brain tumors, for which prognosis remains poor.

NCI sponsors several cooperative clinical trials groups to study pediatric cancers, the largest of which is the Children's Oncology Group (COG). In 2000, NCI facilitated the formation of COG through a merger of the Children's Cancer Group, the Pediatric Oncology Group, the Intergroup Rhabdomyosarcoma Study Group, and the National Wilms Tumor Study Group. Because of this network, accrual to pediatric clinical trials is remarkably high: Among eligible children younger than 5, 90 percent or more are currently treated as part of a clinical trial, compared with less than 5 percent participation in trials by the adult population.

NCI's Pediatric Oncology Branch is a member of COG. Through the

(continued on page 2)

International Ewing Sarcoma Study Under Way

Researchers at NCI have joined forces with investigators across the U.S. and Europe to launch an international clinical trial of a promising new agent against Ewing sarcoma, a rare cancer that affects mostly children, adolescents, and young adults.

The agent, called R1507, is an investigational monoclonal antibody produced by Hoffmann-La Roche that inhibits insulin-like growth factor 1 receptor (IGF-1R). Ewing sarcoma has been linked with mutated genes that promote the production of IGF-1R. Previous phase I studies that included adolescents and young adults demonstrated promising results in Ewing sarcoma patients with treatment-resistant (refractory), progressive disease who had failed multiple standard and "salvage" therapies. In some cases, there have been complete responses to IGF-1R blockers in such high-risk patients.

Dr. Lee Helman, NCI's scientific director for clinical science and a noted expert in pediatric sarcomas, received numerous calls about these early results and met with his colleagues as part of the Sarcoma Alliance for Research through Collaboration several times to hear presentations from companies,

(continued on page 2)

(Director's Update continued from page 1)

Advanced Technology Program at NCI-Frederick and the Office of Science and Technology Partnerships, the Pediatric Oncology Branch has unique access to technology and procedures for genetic analysis, biomarker studies, and targeted therapy development—advances that can be tested in pre-clinical and early-phase clinical trials before moving to the larger extramural community.

NCI's Pediatric Oncology Branch led partnerships that facilitated the successful completion of several therapeutic advances that were first tested in children at the NIH Clinical Center. Among them was the first use of gene therapy, development of "volume photography" to measure growth of neurofibromatosis-1 tumors, and even the first multi-institute hospital unit designed specifically for children at the NIH Clinical Center.

NCI's Pediatric Oncology Branch often works closely with other NIH institutes to cosponsor important pediatric research projects, combining valuable resources and thereby speeding the delivery of new interventions. And collaboration between NCI's SEER Program, Office of Cancer Survivorship, and organizations such as the Lance Armstrong Foundation, help us monitor pediatric survivorship issues such as fertility, second cancers, and race and age-group disparities.

Children usually learn from adults, but sometimes the roles are reversed, and that has been true in pediatric oncology. Some fundamental aspects of cancer treatment today, such as combination chemotherapy and knowledge of tumor suppressor genes, can be traced to research first completed on pediatric cancer patients. Such advances appear in our "Milestones" on page 8.

You may also notice the banner that spans the top of this special issue. It features artwork made by children who have stayed at the Children's Inn at NIH while undergoing cancer treatment, or children who attended therapy sessions led by Dr. Lori Wiener, a social worker and member of our Pediatric Oncology Branch. Both of these programs are highlighted in this special issue.

We at NCI are extremely proud of our Pediatric Oncology Branch and the rich interface of intramural and extramural research in childhood cancers. We always get a special lump in our throats and a smile when we have a successful outcome with one of our special kids.

Dr. John E. Niederhuber
Director, National Cancer Institute

(Ewing Sarcoma continued from page 1)

including Roche, about their IGF-1R blocker compounds for use in a planned phase II study in children and adults aged 12 years and older with relapsed or refractory Ewing sarcoma. They selected R1507 for the current study and will expand this treatment to several other pediatric and adult sarcomas, including rhabdomyosarcoma and osteosarcoma.

"Because these are rare tumors, no single institution can do a large enough study—nor can any one country," Dr. Helman commented, noting that there are only about 200 new cases of Ewing sarcoma diagnosed in the United States each year. "We very quickly engaged our European colleagues who we've collaborated with on a number of previous projects."

The trial got under way at several U.S. cancer centers in December and has already accrued about 30 patients. The study will open shortly at the NIH Clinical Center and at sites in France, Italy, Germany, and the United Kingdom next month.

Dr. Herbert Juergens, professor of pediatric hematology and oncology at the University of Muenster, which is one of the study sites in Germany, said that progress in treatment of Ewing sarcoma "has become very slow" in recent years. Research has achieved long-term survival rates of about 70 percent with standard treatments, which include intensive chemotherapy and "local" interventions of radiation and surgery. "Since then, we seem to have exhausted the intensity of chemotherapy we can administer to the patients," he continued. Instead, hope has focused on finding therapies that target specific receptors in these tumors.

The international trial to test R1507 for Ewing sarcoma "is wonderful," Dr. Juergens said. To find sufficient patients with relapsing disease to produce statistically significant data, he added, "You need to work across the Atlantic Ocean."

Dr. Helman noted, "Over the next several years, we'll have to work hard to see if we can identify genomic profiles or markers that will predict those patients who are more likely to respond to IGF-1R inhibitors and figure out how we might move this to frontline therapy, because it might minimize toxicity" compared with current chemotherapy. ◆

Building on 50 Years of Cooperative Research

COG includes more than 250 institutions in the United States, plus others in Canada, Australia, the Netherlands, Switzerland, and New Zealand.

Fifty years ago, less than 10 percent of children diagnosed with cancer survived long term. Today, that number is almost 80 percent overall. This radical improvement comes largely from the efforts of the Children's Oncology Group (COG), the nation's largest cooperative clinical research group.

The first U.S. pediatric clinical trials group formed in 1955 and received NCI funding in 1956 to address the difficulty of performing clinical trials for children's cancers. In 2000, this group and other U.S. pediatric trial groups merged to form the COG.

"It was recognized that no individual cancer program or children's hospital had the number of patients that could support clinical investigation by themselves," says Dr. Gregory Reaman, professor of pediatrics at The George Washington University and chair of COG. "Cooperation and collaboration were absolutely necessary."

The first cooperative clinical trials focused on chemotherapy for acute lymphoblastic leukemia (ALL), the most common childhood cancer. Rapid improvements for ALL through this system led the groups to expand their research to other hematologic cancers, as well as solid tumors, adding surgery, radiation therapy, immunotherapy, and newer targeted treatments to their experimental regimens.

Today more than 40,000 children are treated on or receive followup as part of COG clinical trials at hundreds of hospitals around the world. In the U.S., "the majority of children for whom there are clinical trials, and who are eligible for those trials, are actually enrolled on clinical trials," says Dr. Reaman. This stands in stark contrast to adults, where only a few percent of eligible patients participate in clinical research.

One of COG's main goals is to increase the number of children treated on clinical trials, but they face many of the same barriers to enrollment encountered by researchers working with adult patients, including scarce funding, lack of access for patients in rural areas, and difficulty in some cases getting insurance companies to cover experimental care.

In addition, explains Dr. Maura O'Leary, administrative officer with COG, for patients who speak English as a second language, the process of informed consent can be complicated. "The ideal would be to print [consent forms] in their own language," she says, so COG has recently started a pilot program to create Spanish-language materials.

In addition to examining the genetics of childhood cancers, COG plans to expand their cancer control, prevention, supportive care, and survivorship research, with international partnerships. "Certain cancers that are rare in the U.S. are more common in other parts of the world, such as Latin America and India," says Dr. O'Leary. "If we can work together to learn how to better treat those cancers, everybody will benefit." ◆

Pediatric Clinical Trial Enrollment By Eligibility

5 and younger: greater than 90%
10 and younger: 75-90%
10 to 15: 50%
Adolescents aged 15 to 19: 15-25%

CureSearch—the foundation affiliated with the COG—recently launched a Spanish-language version of its award-winning pediatric cancer Web site at www.curesearch.org/spanish. ◆

For Research on Risks, Numbers Are a Challenge

Because of the rarity of cancer in children and adolescents, for researchers investigating childhood cancer risks, it's proven difficult to get large enough study populations that can provide reliable, statistically valid conclusions about factors that may only moderately increase cancer risk.

However, through increased collaboration, researchers are retooling their approaches in hopes of getting stronger data on such factors. Their goal is to answer some difficult questions about how a disease like cancer, which is thought to take years or even decades to develop, can take hold in humans within just a few years—or sometimes months—of birth.

"If it's a huge risk, you don't necessarily need enormous numbers to be able to identify the risk factor," explains Dr. Martha S. Linet, chief of the Radiation Epidemiology Branch in NCI's Division of Cancer Epidemiology and Genetics (DCEG). Down syndrome, for example, increases childhood leukemia risk 40-fold. But most childhood leukemia case-control studies, Dr. Linet continues, have identified factors with far smaller risks.

"When these small risks are discovered, it's very difficult to tease apart if they're real, or due to some confounding factors," Dr. Linet says.

The International Childhood Cancer Cohort Consortium is designed to address this problem. Comprising 11 cohorts—none of which was established to study cancer—this international consortium involves more than 70,000 children who are enrolled by their parents before or at birth and, depending on which cohort, will be followed for varying time periods. Each cohort study, while not identically designed, includes detailed questionnaires about potential exposures and the collection of biological samples for molecular analyses.

"Over time," Dr. Linet says, "we're going to be exploring some promising hypotheses that are difficult to study in case-control studies."

Exploration of genetic risks for pediatric cancer has also been limited by small numbers. Such research has mostly been relegated to familial cancers or cancers associated with syndromes such as Li-Fraumeni.

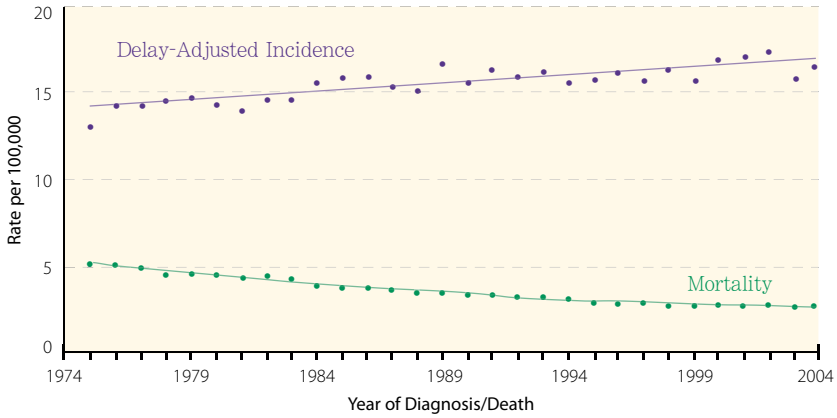
"We've learned a lot from the cancer predisposition syndromes," says Dr. Sharon Savage, an investigator in DCEG's Clinical Genetics Branch. But, because of the rarity of childhood cancers, "We don't yet have a good understanding of how common genetic variants like SNPs (single nucleotide polymorphisms) may affect risk."

Despite the small sample sizes, some headway is being made. In an August 2007 *Cancer Epidemiology, Biomarkers & Prevention* study, for instance, Dr. Savage and NCI colleagues analyzed blood samples from 104 patients with osteosarcoma, which is most prevalent in adolescent boys, and found a two-fold increased risk associated with SNPs in *IGF2R*, a critical gene for growth regulation.

But now they need more numbers. And, with the help of the Children's Oncology Group (COG), they will try to replicate the study with a larger sample size, using 500 to 600 tumor samples from osteosarcoma patients enrolled in COG trials.

Although it's still unclear what this line of investigation will ultimately mean for the prevention or treatment of osteosarcoma, Dr. Savage says, "We're hopeful that it can inform osteosarcoma research as well as other research into cancers in which similar pathways play a role." ◆

SEER Delay-Adjusted Incidence and U.S. Mortality
All Childhood Cancers, 1975–2004
Under 20 Years of Age, Both Sexes, All Races



Technology Drives Search for Childhood Therapies

Childhood cancers are biologically different from those that arise later in life. Cancers in children are more likely to involve developing organs, for instance, or to begin in the prenatal environment.

But whether a cancer occurs early or late in life, the path to more effective and less toxic therapies is essentially the same—it starts with knowing the genetic changes underlying the disease. The tools for discovering these changes may also be the same in childhood and adult cancers, as an innovative public-private initiative hopes to demonstrate.

The initiative, sponsored by NCI and the Foundation for the National Institutes of Health, is called TARGET (the Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments). The goal is to identify and validate therapeutic targets for childhood cancers using the latest genetic and genomic tools, which are the same ones used to develop targeted drugs for adult cancers.

"This project was inspired by the powerful technologies that are available for identifying genetic lesions in cancer cells," said Dr. Malcolm Smith of NCI's Cancer Therapy Evaluation Program and a leader of TARGET. The initiative grew out of a 2005 workshop among cancer specialists from the public and private sectors. A consensus emerged that available technologies could advance research on childhood cancer therapies if sufficient resources were dedicated to the challenge.

A pilot phase of TARGET involving acute lymphoblastic leukemia (ALL) and led by researchers from the University of New Mexico, St. Jude Children's Research Hospital, the Children's Oncology Group, and NCI has produced interesting early results. Profiling gene activity in patient samples revealed a previously unknown subtype of ALL associated with a poor prognosis. Additional studies are underway to search for genomic abnormalities such as extra copies of genes that may underlie the abnormal gene activity detected in the patient samples.

With the diversity of data, the researchers expect eventually to identify the underlying genetic changes in this high-risk subgroup of children with ALL. "The challenge is to identify the genetic lesions that in one way or another are driving the leukemia," noted Dr. Smith.

The initiative is benefiting from lessons learned and tools developed during the implementation of The Cancer Genome Atlas pilot project, which is cataloging genomic alterations in three adult cancers. Both projects will share, for instance, software designed to make the results easily accessible to researchers via the Internet.

The integration of different types of data will be an ongoing process in TARGET. But the researchers believe that by studying relatively large numbers of patients, using consistent research methods, and sequencing between 100 and 150 genes per disease, they will be able to identify critical genes in these cancers that can lead to more effective treatments.

The pilot project is also working on neuroblastoma, with plans to expand to rhabdomyosarcoma and other cancers in the future. ◆

NCI's Division of Cancer Prevention sponsors research to reduce treatment side effects, including mouth sores and nausea and vomiting due to chemotherapy, and hearing loss in children treated with cisplatin. Search the NCI Cancer Research Portfolio using "pediatric research" as a special interest category for other examples. ◆

Children's Inn at NIH

The Children's Inn at NIH provides lodging, healing services, and programs for seriously ill children and their families who are treated across the street at the NIH Clinical Center. To learn more, go to http://www.childrensinn.org. ◆

Testing the Most Promising New Therapies

It is perhaps a good problem to have: Many more experimental cancer drugs enter clinical evaluation in adults each year than can realistically be tested in children, given the small number of children with cancer eligible for early-stage clinical trials.

This means that investigators have to prioritize agents, and their decisions have consequences. If 20 new drugs are available for study, but only one or two can be tested in children each year, then picking an agent that lacks an effect against childhood cancers may delay or prevent an agent that is truly effective from being investigated.

So how can investigators improve their chance of making good decisions about which new agents to bring forward for pediatric clinical testing? One way may be to test candidate agents in the laboratory using pediatric cancer cell lines and animal models. Launched in 2004, the NCI-sponsored Pediatric Preclinical Testing Program (PPTP) is doing this by testing 12 new agents a year against its panel of childhood cancer preclinical models.

The project is an experiment, and it will not be known for several more years how well the models predict anticancer activity in patients. But early results are encouraging. The researchers have provided validation for the strategy by showing that standard chemotherapy drugs have similar effects in the preclinical models as in patients. Importantly, the program has already identified several novel agents that show substantial activity against one or more of the PPTP's childhood cancer tumor panels.

A recent PPTP report in *Pediatric Blood Cancer* describes a drug with anticancer activity against several solid tumors. The drug, SCH 717454, is a monoclonal antibody against the insulin-like growth factor 1 receptor (IGF-1R), which has been implicated in many pediatric solid tumors. Another PPTP publication reported that ABT-263, a small molecule inhibitor of Bcl-2 family proteins, has substantial single agent activity against acute lymphoblastic leukemia cell lines and xenografts.

"The project is providing useful ideas about new agents and combinations of therapies that can be studied in children," said principal investigator Dr. Peter Houghton of St. Jude Children's Research Hospital. The PPTP's research teams have more than 60 animal models and 27 cell lines available for testing, representing most of the more common cancers that occur in children.

The program tries to evaluate new agents near the time that they are entering clinical trials in adults. This allows pediatric preclinical data to be developed while adult phase 1 trials are ongoing so that the preclinical data can then inform decision-making about clinical evaluations of agents tested in children. The adult trials provide information about the drug blood levels that are tolerated in humans, and this information can be modeled in mice to learn whether children are likely to tolerate a dose of the agent that is active against preclinical models.

"The critical issue in terms of translation from the preclinical model to the clinic is using doses in the animal that produce blood levels that you can achieve in the patient," noted Dr. Houghton.

More than 20 pharmaceutical companies have submitted one or more agents for testing. "The willingness of these companies to collaborate with the PPTP has been very encouraging and is central to the success of the program," said Dr. Malcolm Smith of NCI's Cancer Therapy Evaluation Program, who oversees the PPTP. ◆

Childhood Cancer SEER Incidence Rates* by ICCC Group, 2001-2004 Under 20 Years of Age, Both Sexes, All Races

Leukemia	44.2
Lymphoma	23.2
Brain/CNS (2004)	27.4
Neuroblastoma	7.6
Retinoblastoma	3.0
Renal	6.0
Hepatic	2.1
Bone	8.9
Soft tissue	12.0
Germ cell	11.8
Other malignant epithelial neoplasms	16.5
Other	0.6

* Rate per 1,000,000

A Conversation with...Dr. Crystal Mackall

Acting chief of the Pediatric Oncology Branch (POB) in NCI's Center for Cancer Research (CCR)

How does the POB augment work in the extramural community?

Progress against cancer in children has benefited greatly from well-organized cooperative groups in the extramural community that conduct efficient and large randomized trials. However, future progress hinges upon biologic insight and targeted therapies, both of which begin in a basic science laboratory. The focused basic and clinical science conducted in the POB provides the basis and rationale for new therapies, which, if successful, would ultimately be tested in the extramural community.

In what case would a child, adolescent, or young adult come to clinicians in the POB at the NIH Clinical Center in Bethesda for treatment?

The POB conducts clinical trials targeting a variety of childhood cancers and cancer predisposition syndromes for which outcomes with standard therapies are suboptimal. Any child, adolescent, or young adult who is eligible for such trials may be treated in the POB. In some cases, this represents frontline therapy for a newly diagnosed cancer and in others, the therapies are tested in the setting of recurrent disease. A list of POB protocols can be found at http://pediatrics.cancer.gov/protocol.shtml.

Why is pediatric oncology appropriate for patients who would under other circumstances be considered adults?

Cancers that are most common in children but also afflict adults are often treated by pediatric oncologists familiar with the biology and behavior of those diseases. For example, Ewing sarcoma usually occurs in the second decade of life, but may also occur during early and mid-adulthood and, from a molecular standpoint, is the same disease regardless of the age at which it strikes. Treatment regimens used for adults with this disease are the same as those used for children and therefore many current studies for Ewing sarcoma allow both children and adults to be treated on the same trial.

What are examples of cutting-edge research this year in the POB?

Historically, the Molecular Oncology Section of the POB, under the direction of Dr. Lee Helman, contributed seminal work defining the critical role for IGF-1R signaling in pediatric sarcomas. Monoclonal antibodies targeting this receptor have recently entered phase I clinical trials with encouraging results. There is great optimism in the pediatric sarcoma community that this may represent the first biologically based targeted therapy to show activity in these diseases. In a second example, the Hematologic Diseases Section, under the direction of Dr. Alan Wayne, is working closely with investigators from the Laboratory of Molecular Biology at NCI to develop anti-CD22-based immunotoxins to target acute lymphoblastic leukemia (ALL). A recent phase I study showed clinical activity using this approach in patients with recurrent ALL and plans are underway to improve it with a newer, higher-affinity version of the toxin conjugate and combination with standard chemotherapy, which was synergistic in preclinical models. Recurrent ALL remains the single greatest killer of children with cancer and we are very hopeful that this new biologically based therapy will provide new options for patients.

To learn more about the Pediatric Oncology Branch please visit: http://home.ccr.cancer.gov/oncology/pediatric/. ◆

Milestones in Pediatric Oncology

1940s

Remission achieved in pediatric leukemia patients using an antifolate drug, aminopterin

1950s

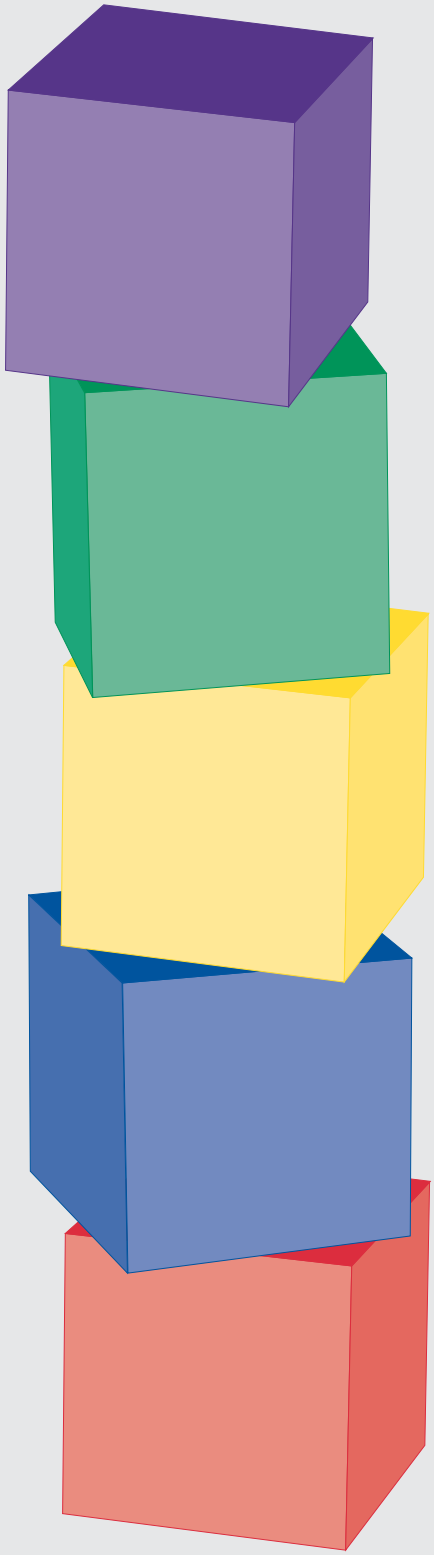
6-mercaptopurine treats pediatric acute lymphoblastic leukemia (ALL) • Combination chemotherapy introduced by NCI researchers • NCI begins funding pediatric cooperative clinical trials

1960s

Dactinomycin first used to treat Wilms tumor • National Wilms Tumor Study Group formed and multi-modal therapy (radiation, chemotherapy, and surgery) first used in pediatric patients • Prophylaxis of occult central nervous system leukemia markedly improves outcome for children with ALL • Laminar airflow technology creates "sterile rooms" for chemotherapy patients

1970s

Intergroup Rhabdomyosarcoma Study Group Committee pioneers repetitive-course, multi-agent chemotherapy for advanced rhabdomyosarcoma • First successful bone marrow transplant (BMT) for leukemia • Knudson describes the 2-hit hypothesis for retinoblastoma to describe genetics and heredity of cancer



1980s

First tumor-suppressor gene, in retinoblastoma, is cloned • MYCN identified as a target of genomic amplification in neuroblastoma • Adjuvant chemotherapy improves relapse-free survival for pediatric osteosarcoma • Different treatment approaches for lymphoblastic lymphoma versus other lymphomas in children are realized • Platinum-based combination chemotherapy improves response rates in pediatric germ cell tumors • National Marrow Donor Program begins ◆

1990s

Autologous BMT and 13-cis-retinoic acid improve event-free survival for high-risk neuroblastoma • Characteristic fusion genes identified for pediatric solid tumors • Combined ifosfamide and etoposide improve outcomes for non-metastatic Ewing sarcoma • Treatments achieve long-term survival rates of 80–90% for advanced Burkitt lymphoma • Risk-directed therapy becomes treatment paradigm for children with ALL • Genetic test for rare thyroid cancer enables prophylactic thyroidectomy before the age of 2 • NCI-funded Childhood Cancer Survivors Study begins

2000s

Four legacy research groups merge as the Children's Oncology Group (COG) • COG publishes long-term follow-up guidelines for pediatric cancer survivors • Imatinib added to intensive chemotherapy improves early outcomes for Ph+ ALL • 5-year survival rates for children with cancer (age 0–14 years) approach 80%

Improvements Needed for Adolescents and Young Adults

Compared with advances achieved for younger children over the past 30 years, there has been a relative lack of progress in identifying more effective treatments for adolescent and young adult (AYA) cancer patients. Cancer survival rates for AYA patients, who are those diagnosed with cancer at ages 15 through 39, have seen little or no improvement for decades. This concern led NCI and the Lance Armstrong Foundation (LAF) in 2005–2006 to convene a Progress Review Group (PRG) to evaluate the issues behind this bleak trend.

In its final report, the PRG described factors that contribute to the problem: high numbers of uninsured AYAs and a tendency for kids and young adults with cancer to fall into a "no man's land" between pediatric and adult oncology practices. The panel concluded that "a major, ongoing AYA [oncology]-specific research initiative emphasizing AYA clinical trials and outcomes research is urgently needed."

Now a trans-NCI study of AYA patients, led by the Division of Cancer Control and Population Sciences, is under way in seven SEER registries with support from the LAF. The study will investigate patterns of care and outcomes for patients aged 15–39 with acute lymphoblastic leukemia (ALL), lymphoma, sarcoma, and germ cell cancers through a patient survey and medical record examination. The study will assess treatment, physician and facility characteristics, clinical trials participation, barriers to care, as well as the impact of cancer on physical symptoms, psychosocial experiences, financial issues, and quality of life.

Dr. Malcolm Smith of NCI's Cancer Therapy Evaluation Program also points to clinical trials for AYA patients with ALL. "Recent publications have reported that adolescents and young adults treated on pediatric clinical trials have had better outcomes than similarly aged AYA patients treated using adult protocols for ALL," he noted.

One of the trials cited by Dr. Smith is being conducted by the Dana-Farber Cancer Institute (DFCI) Consortium, which presented preliminary findings at the American Society of Hematology annual meeting last year. Current chemotherapy regimens in children with ALL produce event-free survival (EFS) rates of greater than 80 percent compared with EFS rates of 30–40 percent in adults with ALL. DFCI Consortium researchers reported that for patients aged 18–50 with ALL who were treated with an intensive pediatric regimen, the estimated 2-year EFS was 72.5 percent. Although the study requires longer follow up, the preliminary results suggest that intensive treatment strategies for young adults with ALL could represent a major therapeutic advance.

Another study to improve outcomes for young adults with ALL, CALGB-10403, is under way with the NCI-sponsored adult cooperative groups. The study adopts the treatment approach for ALL that is used by the Children's Oncology Group (COG). A retrospective analysis conducted as part of the trial compared outcomes of ALL patients aged 16–20 who were treated by either the CALGB Intergroup physicians or by pediatric COG specialists.

"What we found was that there was tremendous disparity in outcomes and that those AYA patients who were treated on pediatric regimens had significantly improved disease-free survival and overall survival," said Dr. Wendy Stock, associate professor at the University of Chicago Department of Medicine. "It was almost a 30 percentage point difference. That was very disappointing and it stimulated a lot of questions about why this might be."

The Intergroup retrospective analysis, which will be published in *Blood*, found key differences in both the dose intensity of the drugs used and in the treatment schedules adopted by pediatric versus adult cancer specialists. "In addition to differences in the protocol design and schedule, the outcome disparity also raises questions about protocol compliance and whether adult medical oncologists and the patients that they treat adhere to protocols as rigorously as the pediatric oncologists and their patients," Dr. Stock noted. "We hope to begin to gather specific data about treatment compliance in addition to exploring the feasibility of using this approach to improve outcomes of AYAs with ALL in the adult cooperative groups." ◆

The 2008 NCI SEER Cancer Statistics Review includes a new chapter on AYA cancers and will be posted online in May at http://seer.cancer.gov/ ◆

Caregivers are Key for Helping Children Survive Cancer

In addition to watching a loved one undergo difficult treatments, families of children with cancer must deal with disruption of normal life, travel to treatment centers, arranging childcare, finances, and other challenges. The cumulative effects can have serious consequences for quality of life during treatment and after it ends.

"We realize now that in order to provide our pediatric patients with the services that they need, we have to see these children in the context of their families and their communities, and integrate each of these dimensions so they can return home with the support, tools, and coping strategies to survive cancer," explains Dr. Lori Wiener, head of the Psychosocial Section and coordinator of the Psychosocial Support and Research Program in NCI's Pediatric Oncology Branch.

She hopes that some of the research under way through her program, which has developed resources and practice models for treatment centers and families, can help people who are looking for ways to handle these challenges. Psychosocial support within the pediatric oncology program begins with social workers who contact patients as soon as they are recommended for a clinical trial at NIH, and who maintain contact with these families one-on-one throughout the course of their treatment.

Many of these families stay at the Children's Inn at NIH, where support programs compliment services at the Clinical Center, including play, art, and music therapy; support groups and workshops; psychiatric consultation; counseling; camp programs; school programs and vocational testing; pain and palliative care services; spiritual ministry; and bereavement programs, among others.

Dr. Lori Wiener's Coffee, Tea, and Chat program, started in 2005, allows parents and children to meet as a group and discuss their concerns with clinical experts.

Psychotherapy for children in clinical trials also addresses fear and anxiety due to being far from home, new treatments, and invasive procedures. "It's horrifying to see a panic-stricken child trying to deal with an impending bone marrow transplant, or any kind of needle stick," says Dr. Jimmie Holland, a psychiatrist and Wayne Chapman Chair in Psychiatric Oncology at Memorial Sloan-Kettering Cancer Center, which has the country's largest training program in this field. "The experience upsets anyone who comes near it. But if you can help these children and their family members prepare for the rigors of treatment, using behavioral techniques that are proven, you can give patients and their families a sense of control and diminish panic in these situations."

Drs. Holland and Wiener have worked together on resources that outline psychosocial issues and solutions that are so critical to successful cancer care, some of which are based on a report commissioned by the Institute of Medicine, *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*, as well as a reference book that will soon be available from the American Psychosocial Oncology Society, *Quick Reference for Pediatric Oncology Clinicians: The Psychiatric and Psychological Dimensions of Pediatric Cancer Symptom Management*, for which Dr. Wiener is lead editor.

Dr. Wiener's program has also developed tools, including several for the siblings of cancer patients: a workbook titled *This is MY World*, another titled *Brothers and Sisters—We're in This Together*, and a customizable board game available later this year.

After children complete their cancer treatment and leave the Clinical Center, they are connected with the support network in their local communities. But their relationship with staff at NIH can last a lifetime. Even when a child dies, their family members are considered cancer survivors, Dr. Wiener explains, and she is in touch with them each year on the anniversary of their loss. "There's a sense that we've lived through this life-altering experience together," Dr. Wiener says, "and a special connection often arises between families and the health care providers who traveled that journey with them." ◆

Pediatric Cancer Survivors Need Long-Term Follow-Up

The very high cure rate in pediatric oncology has not been achieved without a cost: treatments that save children's lives can also damage developing organs, causing a wide array of health problems that may not surface for many years.

Current understanding of the extent of "late effects" in childhood cancer survivors—health problems related to cancer treatment that occur months to years after treatment ends—has emerged largely from the Childhood Cancer Survivors Study (CCSS). Since 1994, this NCI-funded research project has followed a cohort of 20,000 people who were diagnosed with cancer as children between 1970 and 1986 and survived at least 5 years.

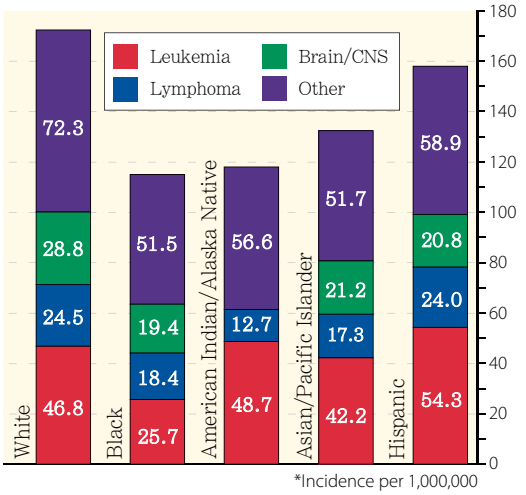
In a study published in the *New England Journal of Medicine* in 2006, which looked at outcomes in more than 10,000 survivors, CCSS researchers found that almost two-thirds of patients reported at least one chronic health problem, one-quarter had a severe condition, and almost one-quarter had three or more chronic health problems. Late effects reported most frequently in this study were second cancers, cardiovascular disease, kidney disease, musculoskeletal conditions, and endocrine abnormalities. The risk of developing a health problem related to cancer treatment in childhood increased over time.

Women face higher risks than men for late effects including breast cancer, cognitive dysfunction, heart disease, and hypothyroidism. Other factors influencing late effects include age at diagnosis, type of cancer, and types of treatment received. Radiation treatment, especially to the brain—and, in women, the chest—carries a high risk of long-term effects.

"Both the magnitude and the diversity of the long-term health effects have been striking," says CCSS principal investigator Dr. Les Robison of St. Jude Children's Research Hospital in Memphis. "At 30 years after their diagnosis, more than 70 percent of childhood cancer survivors have a late-effect chronic health condition."

Results from CCSS studies are now informing the development of guidelines for appropriate follow-up care for childhood cancer survivors, adds Dr. Robison. The limited data so far available suggest that most survivors do not receive the recommended follow-up care. CCSS researchers are now planning several new studies looking at how to ensure more survivors obtain follow-up care so that late effects are detected as early as possible.

Childhood Cancer
SEER Incidence Rates*
by ICCC Group and Race Ethnicity, 2001–2004
Under 20 Years of Age, Both Sexes



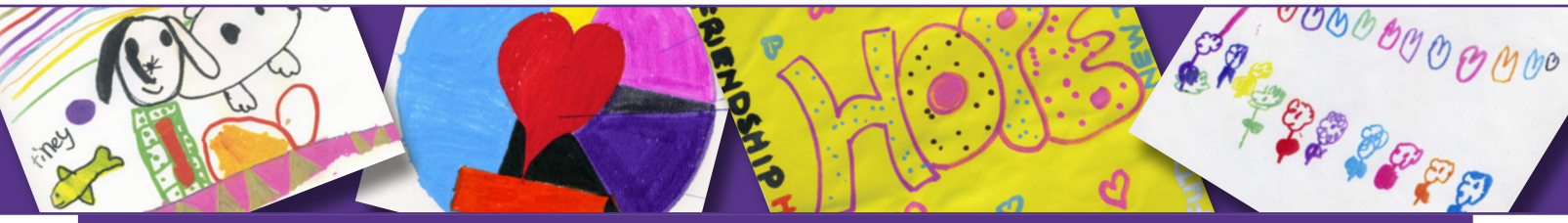
*Incidence per 1,000,000

CCSS data are available to researchers studying important questions in pediatric cancer survivorship through the St. Jude Web site (www.stjude.org/ccss). To date, the CCSS has generated more than 75 publications in the peer-reviewed literature.

Treatments for childhood cancer have changed a lot since the CCSS cohort was treated in the 1970s and early 1980s. To learn about the long-term effects of these newer therapies, researchers are now expanding the CCSS cohort by recruiting 20,000 survivors treated for childhood cancer between 1987 and 1999 who have survived at least 5 years.

In other efforts, researchers are developing new tools, such as the Passport for Care, to help clinicians and childhood cancer survivors be more aware of and communicate with each other about the long-term effects of cancer treatments, as well as decision aids to help survivors weigh the costs and benefits of treatment approaches.

"Childhood cancer survivors are in the vanguard in terms of our understanding of the impact of living long-term after cancer treatment," says Dr. Julia Rowland, director of NCI's Office of Cancer Survivorship. "The challenge is to ensure that they are appropriately followed across their lifetimes to minimize cancer's late adverse impacts and maximize these survivors' overall health." ◆



Other Helpful Resources

General Information about Childhood Cancer

The main portal for information from NCI is at http://www.cancer.gov/cancertopics/types/childhoodcancers

Children's Oncology Group (COG) treatment and follow-up guidelines http://www.survivorshipguidelines.org/

Reports on Childhood Cancer Incidence from NCI

Incidence and Survival among Children and Adolescents: 1975–1995
http://seer.cancer.gov/publications/childhood/

Epidemiology in Older Adolescents and Young Adults 14 to 29 Years of Age
http://seer.cancer.gov/publications/aya/

SEER Cancer Statistics Review, 1975–2004
http://www.seer.cancer.gov/csr/1975_2004/

New Malignancies among Cancer Survivors: 1973–2000
http://www.seer.cancer.gov/publications/mpmono/

Clinical Trials and Treatment Centers

A list of COG members is at http://www.curesearch.org/resources/cog.aspx and a database of clinical trials is at http://www.cancer.gov/clinicaltrials

Training at NIH

Pediatric Hematology-Oncology Fellowship Training Program
http://www.cc.nih.gov/training/gme/programs/pediatric_hematology_oncology.html

Pediatrics/Medical Genetics Residency Training Program
http://www.cc.nih.gov/training/gme/programs/pediatrics_medical_genetics.html

Advanced Studies Program in Pediatric Oncology: Contact Dr. Alan Wayne at waynea@mail.nih.gov or 301-496-4256

Risk-reduction Programs

From the NCI Division of Cancer Control and Population Sciences
http://cancercontrol.cancer.gov/cancer_resources.html

And from the National Heart, Lung, and Blood Institute
http://www.nhlbi.nih.gov/health/public/heart/obesity/wecan/

Advocacy Groups

CureSearch National Childhood Cancer Foundation
http://www.curesearch.com/

Children's Cause for Cancer Advocacy
http://www.childrenscause.org/

Candlelighters Childhood Cancer Foundation
http://www.candlelighters.org/

The National Children's Cancer Society
http://www.children-cancer.com

Pediatric Brain Tumor Foundation
http://www.pbtfus.org/

Children's Brain Tumor Foundation
http://cbtf.org/cms/

American Brain Tumor Association
http://www.abta.org/

National Brain Tumor Foundation
http://www.braintumor.org

The Childhood Brain Tumor Foundation
http://www.childhoodbraintumor.org/

Leukemia & Lymphoma Society
http://www.leukemia-lymphoma.org/hm_lls

National Children's Leukemia Foundation
http://www.leukemiafoundation.org/