A Multidisciplinary Approach to Cancer Prevention and Control

Thanks to decades of research and treatment, the population of childhood cancer survivors is increasing. However, as these survivors age, the delayed effects of cancer and its treatment threaten their health, longevity, and quality of life.

Young survivors of childhood cancer face chronic illnesses that are more typical of the elderly: reduced bone mineral density, osteonecrosis, diabetes, cardiovascular complications, and limited physical mobility. Late adverse effects of surgery, chemotherapy, and radiation therapy are experienced by roughly two thirds of childhood cancer survivors and are severe or life-threatening in 25%.

The severity of many of these conditions may be lessened through appropriate diet, regular exercise, and other healthy lifestyle choices.

How do young survivors react to the many risks they face? “Contrary to what you might expect, having been treated for cancer does not strongly increase survivors’ risk-avoidance behaviors later in life,” explains Cheryl Cox, PhD, of the newly created Department of Epidemiology and Cancer Control at St. Jude. “One may say that ‘teens will be teens,’ but these kids are not hearing about prevention methods for more than 5 years after diagnosis. We need to get that message into...”

3T MRI – Physics and Medicine in Motion

When clinicians and physicists get together to talk about magnetic resonance imaging (MRI), it’s enough to make your head spin—well, maybe not your whole head, just the protons!

The introduction of ultra–high field MRI technology (3-Tesla or 3T MRI) is changing the way we think about imaging in medicine, but not without strong collaborative efforts between clinicians and physicists. At St. Jude, where translational research is the norm, the installation of 3T MRI technologies is an opportunity to explore new worlds.

Fred Laningham, MD, of the Department of Radiological Sciences, is excited about the benefits ultra–high field MR technology will provide to patients at St. Jude. He explains, “With increased MRI signal strength relative to noise, we hope to gain greater clinical sensitivity and achieve better diagnostic value.”

The signal-to-noise ratio (SNR) upon which an MR image is constructed increases with the static field strength of the polarizing magnet. This means that the SNR in 3T MRI can be almost 2 times that of 1.5T MRI, the standard...
their heads earlier!" The ideal solution would be to introduce prevention strategies in innovative ways that are heard, understood, and adopted at the time of diagnosis.

Throughout and after cancer treatment, the primary-care physician can have an enormous influence on the patient’s long-term health and well-being by simply encouraging a healthy diet and physical activity. It is also essential to ensure that survivors understand the physical changes that can result from the cancer experience and to encourage self-examination (e.g., breast and skin examination) in high-risk groups treated with radiation to ensure early identification of a possible second cancer. In addition to overall health promotion, it is important to encourage them to avoid high-risk behaviors (such as smoking, over-consumption of alcohol, and experimentation with drugs). Genetic counseling and education about sexual activity is important when cancer is genetically linked to a family history. Lifestyle changes could not only allow survivors to lead healthier lives but also improve their sense of well-being. The family physician is in a unique position because of his or her individual knowledge of the child. The physician should not focus only on the patient’s medical status but should also consider the child’s personality, motivation, present and past behaviors, home and community environment, lifestyle, and school activities.

The creation of the Department of Epidemiology and Cancer Control and the role that its members play in the Cancer Prevention and Control Program at St. Jude strategically places the institution as one of the few cancer centers cont., p. 3

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The Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG LTFU Guidelines) have been made more user-friendly by conversion to a flip-chart format. The goals of the guidelines are to educate health care providers and patients about late effects of cancer treatment and to increase survivors’ comfort level through an understanding of their risks. These guidelines facilitate early detection of late effects, promote healthy lifestyles, and guide ongoing monitoring of health status and timely intervention for late effects. They provide a practical tool for translating knowledge into clinical practice. Physicians can determine at a glance what factors they should be most concerned about by looking at factors such as a patient’s current age, sex, age at diagnosis, cancer site, treatment modality, and lifestyle. Scoring and references are now integrated into the charts and are readily accessible. Information for males and females is now separate, allowing easier access to sex-specific information. (Shown: COG LTFU Guidelines, V2.0 [March 2006], p. 9)

Visit [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org) to view the improved guidelines.
St. Jude Clinical Trial Protocols

Below is a subset of the Phase I, Phase I/II, and Phase III clinical research protocols currently conducted at St. Jude. Phase I studies use are determined to the maximum tolerated dose (MTD) and toxicity of the study drug(s). Phase II studies utilize the MTD to begin studying the drug treatment’s effectiveness in a limited, controlled manner. Phase III studies compare the effectiveness of the study drug(s) with the effectiveness of a standard therapy. To find out more about the objectives of the studies below and their eligibility criteria, visit www.stjude.org/protocols, send an e-mail message to protocolinfo@stjude.org, or call the toll-free Physician Referral Line, 1-866-2ST-JUDE (1-866-278-5833).

SJBG07: A Phase I trial of vandetanib administered with local radiation therapy.
- Eligibility: Pediatric patients with newly diagnosed diffuse brainstem glioma.
- Principal Investigator: Alberto Broniscer, MD

TOTALXV: A total therapy study using new combinations of anti-cancer drugs.
- Eligibility: Patients with newly diagnosed acute lymphoblastic leukemia (ALL)
- St. Jude Principal Investigator: Ching-Hon Pui, MD

AML02: A collaborative trial comparing remission rates in children receiving different doses of cytarabine during induction therapy and effects of the use of getuzumab ozogamicin (GO).
- Eligibility: Children and teens with newly diagnosed acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or biphenotypic leukemia.
- Principal Investigator: Jeffrey E. Rubnitz, MD

ZD1839: A Phase I study of ZD1839 (Iressa®) in combination with irinotecan and vincristine. Cefixime and cefpodoxime will be added to the combination to determine whether the irinotecan dose can be increased without producing additional toxicity.
- Eligibility: Pediatric patients with solid tumors that are refractory to conventional therapy or for which no conventional therapy exists.
- St. Jude Principal Investigator: Wayne Furman, MD

RAD001: A Phase I/II study of RAD001C (everolimus) to establish the maximum tolerated dose and antitumor activity.
- Eligibility: Phase I: Pediatric patients with recurrent or refractory solid tumors or brain tumors. Phase II: Patients with recurrent or refractory rhabdomyosarcoma or non-rhabdomyosarcoma soft-tissue sarcoma.
- Principal Investigator: Maryam Fouladi, MD

Patient Care

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that specialize solely in the treatment of childhood cancers. “We strive to nurture the cross-fertilization of ideas and take a multidisciplinary approach to studying appropriate, early intervention,” says Dr. Les Robison, Chair of the department. He clarifies by adding, “Cancer prevention and control is not just about the prevention of disease or the control of the detrimental late effects of treatment. It is about intervention, and intervention requires that we know the epidemiology (frequency and distribution) of the disease, its outcomes, and the role of the patient’s environment.”

The large St. Jude patient base provides a unique opportunity for survivorship research. The new department provides a physical, creative, and collaborative environment that nurtures a multidisciplinary approach to the study of early intervention strategies. A core element of the department is the After Completion of Therapy (ACT) Clinic, headed by Melissa Hudson, MD, a pediatric oncologist at St. Jude. The ACT Clinic participates in protocol-driven clinical studies conducted by 12 St. Jude investigators. Topics under study include assessment and treatment of attentional deficits in survivors of brain tumors; the interaction between organ senescence and treatment toxicity; factors that predispose patients to adverse health outcomes, including physical impairment and impaired quality of life; interventions designed to alter risk-related behaviors; factors related to skeletal complications; and patient and family adjustment.

As Dr. Cox sums it up, “We have an opportunity, by using strategic behavioral interventions, to ease the transition through treatment for some childhood cancers and to relieve some of the inevitable symptoms of therapy. At the same time, we lay the foundation for lifelong healthy behaviors that will ultimately minimize long-term late effects. All of this can start at the time of diagnosis.”

Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers are available at www.survivorshipguidelines.org
in clinical care today. The increased SNR at 3T essentially offers “clinical currency” to spend in the clinical arena. Robert Ogg, PhD, whose interest is functional MRI (fMRI), explains, “You can either spend this currency by saving time in the scanning process or you can spend it to optimize the quality of the image. At St. Jude, there is never any question. It is the quality of the image, and hence the diagnostic value, that we are after.” With 3T, you get more sensitive fMRI, than is possible at 1.5T. To really “cash in” requires close collaboration between physicians and physicists to revise imaging protocols and adjust MRI practices.

“Some scientists talk about greater image resolution, but it’s more about shorter french fries!” says Ralf Loeffler, PhD, MRI physicist in the Department. He explains that a 3T MRI image, like that of its 1.5T predecessor, allows the creation of a 3-dimensional image by stacking cross-sectional image slices. Each slice is made up of an array of vertical columns, or voxels (like a stack of french fries standing in a carton) representing radiofrequency data collected after spinning protons relax and release energy after being exposed to temporally and spatially varying magnetic fields. Although the in-plane resolution is much better than the resolution across the thickness of the slice, the advantage of 3T MRI is the thin slices it allows—as thin as 1 to 3 mm, as compared to the 4- to 5-mm slices at 1.5T. “The thinner the slice, the shorter the french fry,” Dr Loeffler explains, “and since signal is averaged over a shorter distance, smaller structures are more conspicuous, offering greater clinical sensitivity.”

Reducing the image slice thickness by roughly 30% may allow detection of smaller tissue elements that would have been averaged out in the data collection processes of a 1.5T MRI. As Dr. Laningham explains, “This means that smaller foci of recurrent or residual tumor may be better detected by using 3T MRI.”

Claudia Hillenbrand, PhD, another researcher in the Department, stresses that although 3T MRI technology is not uncommon these days, very few centers have combined it with the Total imaging matrix (Tim®) system developed by Siemens, which allows as many as 32 radiofrequency channels of data collection. St. Jude is among just a handful of institutions worldwide that are developing this technology solely to benefit children and to study pediatric cancer, but the spin-off applications for clinical diagnosis are virtually endless. Dr. Laningham explains, “It’s exciting to think that 3T MRI might allow earlier detection of recurrent neoplastic disease (cancer) or might better define the neuronal basis of behavioral changes in pediatric patients undergoing chemotherapy and radiation therapy. Researchers in our division have also begun to study vascular abnormalities in children with sickle cell disease using 3T MRI. We hope that this new technology will translate into earlier and more timely adjustments in clinical strategy and result in better outcomes and an improved quality of life for these patients.”

Greater clinical sensitivity in 3T MRI. The stronger magnet used in 3T MRI makes it possible to generate a thinner image slice while maintaining an ideal signal to noise ratio from this smaller volume. With a thinner image slice, the voxel (a 3-dimensional volume of imaged tissue) is shorter and the resultant point on the image provides higher resolution information. This is true because shorter voxels provide a higher percentage of signal related to the tissue of interest than can be accomplished with thicker sections.
A Nasal Spray to Prevent Ear Infection

In mice, treatment with a nasal spray containing a bactericidal virus enzyme prevents acute otitis media. The treatment may have the same protective effect in children. About 50% of children are colonized by *Streptococcus pneumoniae*, which causes acute otitis media after viral infection. The nasal spray works by reducing or eliminating nasopharyngeal pneumococcal colonization. This success suggests that it could significantly reduce the incidence of otitis media, which is the leading cause of antibiotic prescription for preschool children in the U.S.

Researchers at St. Jude and Rockefeller University based the treatment on lysin, which is used by phage viruses to release progeny from infected gram-positive bacteria. The study used a mouse model developed at St. Jude that simulates for the first time the way in which acute otitis media develops in children. The mice were nasally colonized with pneumococci, then inoculated with influenza virus. Otitis media developed in 80% of saline-treated control mice but in none of the mice treated with lysin.

The lysin treatment may also help to prevent secondary pneumococcal pneumonia. “Secondary bacterial infections cause about 25% of all deaths during the flu season,” said Jon McCullers, MD, lead researcher at St. Jude. Eliminating this secondary infection could offer important protection to infants and the elderly.

“The nasal spray may eventually be used during the flu season or after someone is infected with the flu virus,” said Dr. Vincent Fischetti, lead Rockefeller University team member. “This might truly be a case in which an ounce of prevention is worth a pound of cure.”


Predicting Osteonecrosis after Chemotherapy

Osteonecrosis of the weight-bearing joints is a serious long-term complication of therapy for childhood leukemia or lymphoma. St. Jude investigators have found a way to predict which patients are likely to experience the worst outcomes. They found that if more than 30% of the capital femoral epiphysis has deteriorated, the patient is at high risk of joint collapse within 2 years.

Corticosteroids are a necessary component of chemotherapy for pediatric leukemia and lymphoma, but they are implicated in osteonecrosis. “Being able to predict which children are likely to experience serious bone deterioration will help investigators identify and monitor survivors at particularly high risk,” said Sue Kaste, DO, the study’s senior researcher.

Collapse of the femoral head causes severe pain that can leave a patient wheelchair-bound without arthroplasty. “Degenerative joint changes are especially devastating in a young person,” Kaste said, “and many patients will require future revision or replacement of their prostheses.”

The study reviewed the medical records and MRI images of 80 patients with osteonecrosis to identify factors associated with subsequent joint collapse and arthroplasty. Twenty-three patients (29%) eventually underwent arthroplasty of one or both hips, an average of 1.3 years after diagnosis of osteonecrosis. The worst prognosis was associated with necrosis of more than 30% of the femoral head; 80% of these joints collapsed within 2 years, and 50% required arthroplasty.

“We want survivors to have the best quality of life possible,” Kaste said. “We examined extensive data accumulated at St. Jude over the years to help identify patients who will need the closest monitoring.” The investigators also plan to conduct prospective studies to explore therapies that may prevent damage and preserve hip function.

What’s New on Cure4Kids

Cure4Kids (www.cure4kids.org) is a Web site dedicated to improving health care for children in countries around the globe. Cure4Kids provides continuing education and global communication tools to health care professionals who treat children with cancer and other catastrophic diseases. Cure4Kids contains hundreds of seminars, courses and conferences. All material can be freely used and downloaded for reference and educational purposes. Recent seminars include:

- Acute Lymphoblastic Leukemia: Recent Advances
- Long-Term Follow-Up of Leukemia Survivors
- Influenza from Genome to Vaccine
- Retinoblastoma Treatment and Translational Research
- Hodgkin Lymphoma: A Historical Perspective
- Approach to Mild Bleeding Disorders
- Hereditary Cancer Syndromes – Genetic Considerations in Patient Assessments
- Pedigree Construction and Interpretation
- Pediatric Pain Assessment and Management

Cure4Kids has recently launched Oncopedia to enhance our pediatric hematology/oncology content and increase interactivity among users. The name, intent and scope of Oncopedia are based on those of Wikipedia (http://en.wikipedia.org/). Oncopedia’s content is compiled using online submissions from Cure4Kids users. The content consists of complex hematology/oncology cases and images, specific questions about patient management and interesting presenting features (including illustrations and imaging of patients’ clinical characteristics and pathology). An international editorial board reviews all contributions. Cases chosen for Oncopedia are posted with expert commentary from our editorial board and opened for online, moderated discussion. Explore Oncopedia at www.cure4kids.org

Cure4Kids has attracted 11,460 users from 156 countries.

Save the Date

All conferences are held at St. Jude Children’s Research Hospital.

St. Jude Affiliate RN/CRA Conference
November 2–3, 2007

St. Jude Biomedical Symposium
November 30, 2007

St. Jude Pediatric Infectious Diseases Symposium
February 1–2, 2008
Referrals

St. Jude Children’s Research Hospital welcomes referrals of children and adolescents with newly diagnosed, untreated or suspected cancer; HIV infections; or certain hematologic, immunologic, or genetic diseases. Patients are accepted based on the eligibility to enroll in an open St. Jude clinical research protocol.

Patients with certain genetic disorders, hematologic, immunologic diseases or HIV infection may be accepted anytime in their disease history based on protocol eligibility or potential to contribute to research projects. Other patients who have received treatment elsewhere may be considered on an individual basis, if they are eligible for a St. Jude clinical trial. Patients are enrolled on clinical trials designed to provide the best available care while answering important research questions.

All children accepted for treatment at St. Jude are treated without regard to the family’s ability to pay. The American Lebanese Syrian Associated Charities (ALSAC, the fund-raising organization that supports St. Jude) cover all costs of therapy, signs of recurring disease, or other questions related to the care of patients on St. Jude clinical trials and survivors.

Consultations

St. Jude provides free formal consultations to treating physicians about difficult diagnostic or medical management questions. For a formal consultation, the physician should send complete medical information, such as detailed medical history, copies of relevant diagnostic imaging evaluations, and pathology/histological material. The hospital’s multidisciplinary groups will discuss the case and offer recommendations. St. Jude does not bring patients to Memphis for consultations unless they are likely to be eligible for a St. Jude protocol.

Physician Referral Line

Phone: 1-866-2ST-JUDE (1-866-278-5833), fax: 901-495-4011, e-mail: referralinfo@stjude.org, Web: www.stjude.org/referringmds
This is the panoramic dental x-ray of a 14-year-old survivor of acute myeloid leukemia (AML). As a child, he received chemotherapy and high-dose radiation to support a successful bone marrow transplant.

Question: How has this patient’s life-saving clinical therapy affected his dental development?

Young patients who undergo chemotherapy and high-dose irradiation of the head and neck to prepare for bone marrow transplantation or as part of their treatment for Hodgkin’s disease, nasopharyngeal carcinoma, or retropharyngeal rhabdomyosarcoma are likely to experience severe stunting of the dental roots. The risk is greater in very young children. Root stunting can also lead to delayed shedding of primary teeth. Unshielded high-dose irradiation of the mouth area can also increase the risk of cavities by decreasing saliva production and altering the normal pH of the mouth. More frequent dental examination during and after therapy cannot prevent these sequelae but can help improve dental health through timely intervention.

ANSWER: Young patients who undergo chemotherapy and high-dose irradiation of the head and neck to prepare for bone marrow transplantation or as part of their treatment for Hodgkin’s disease, nasopharyngeal carcinoma, or retropharyngeal rhabdomyosarcoma are likely to experience severe stunting of the dental roots. The risk is greater in very young children. Root stunting can also lead to delayed shedding of primary teeth. Unshielded high-dose irradiation of the mouth area can also increase the risk of cavities by decreasing saliva production and altering the normal pH of the mouth. More frequent dental examination during and after therapy cannot prevent these sequelae but can help improve dental health through timely intervention.