Preventing and Treating Relapse of Childhood Leukemia in the Central Nervous System

Clinicians have achieved a high success rate in treating childhood leukemias: the probability of 5-year event-free survival for acute lymphoblastic leukemia is up to 86%, and that of acute myeloid leukemia is approximately 65% at St. Jude. “Now, a major challenge is to improve treatment of central nervous system (CNS) leukemia in these patients,” said Ching-Hon Pui, MD, Chair of Oncology and coauthor of a recent review on the current state and future direction for such treatment in the March 2008 issue of The Lancet Oncology.

A few (2%-3%) patients present with overt CNS leukemia at the time of diagnosis, and some (3%-8%) experience relapse in the CNS during or after treatment. “Because the control of cancer in the bone marrow has improved so much, CNS relapse has become proportionally more important,” Pui said. “If we are to further increase the cure rate and improve the quality of life of our patients, we need to concentrate on preventing CNS relapse.”

Intrathecal chemotherapy is preferable to radiation therapy

A key goal toward preventing CNS leukemia is improving chemotherapy and avoiding the use of cranial irradiation.

Dr. Ching-Hon Pui
Chair, Department of Oncology

Joseph H. Laver, MD, MHA, has joined St. Jude as Clinical Director and Executive Vice President.

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Although radiation therapy effectively prevents and treats CNS relapse, its effectiveness is offset by the associated severe side effects (e.g., stunted growth, neurocognitive problems, multiple endocrinopathies, and secondary cancers). According to Pui and his co-author, Scott Howard, MD, Oncology, clinicians should avoid using radiation therapy in all patients, even those at high risk of relapse. In St. Jude Study XIIB (1994–1998) in which only 12% of patients received radiation, less than 2% of patients developed CNS relapse. With more effective systemic and intrathecal therapy, conceivably CNS control can be maintained without the use of radiation. Thus, since 1999, radiation has been reserved for the treatment of relapse in St. Jude studies. Moreover, the salvage rate for CNS relapse in patients who did not receive prior radiation therapy is very high (~80%). Finally, it is difficult to successfully treat patients who experience relapse in the bone marrow or CNS after undergoing radiation therapy.

Pui and Howard have found that the optimal regimen for preventing and treating CNS relapse is the so-called “triple treatment” in which three anti-cancer drugs, methotrexate, cytarabine, and hydrocortisone, are used in combination. Multiple studies have shown that triple treatment avoids the side effects of irradiation while achieving comparable treatment success. The intrathecal approach used by Pui and Howard allows the drugs to circulate in the cerebrospinal fluid. However, care must be taken to avoid traumatic lumbar puncture, an adverse event that increases the likelihood of CNS relapse. Even with such success, ongoing studies are still exploring the best strategies for intrathecal and systemic chemotherapy treatments.

Benefit of Bone Marrow Transplantation Remains Unproven

One approach to treating CNS relapse is bone marrow transplantation in which the patient is given massive chemotherapy and radiation to eradicate bone marrow cells, including the leukemic cells. The patient’s bone marrow is then restored by transplanting stem cells from a donor. “However, there are no conclusive trials that show this approach to be superior to intensive chemotherapy,” Pui said, “so we continue to use intensive chemotherapy instead of transplantation to treat patients with CNS relapse at St. Jude.”

Summary

Leukemia relapse in the CNS may be the tip of the proverbial iceberg. Although we can easily see leukemia in the CNS, the disease may also be hidden in the bone marrow. The key to successfully treating childhood acute leukemia is to control the disease at both sites, otherwise the patient may experience subsequent leukemia relapse in the bone marrow and be worse off. At St. Jude, our acute leukemia protocols involve detecting subclinical CNS leukemia early and treating it aggressively to control disease at both sites and ensure excellent outcomes for our patients.

In conclusion, irradiation of the brain should not be used for preventive purposes. It should be used only for the treatment of CNS relapse in patients who really need it to survive. In their review, Pui and Howard emphasize the importance of continuing research. Despite the improved management of children with leukemia, more effective chemotherapy is clearly needed for patients who either have or are at a high risk of CNS relapse.

Joseph H. Laver, MD, MHA, has joined St. Jude as Clinical Director and Executive Vice President

As Clinical Director and Executive Vice President, Dr. Laver will lead the overall patient care program at St. Jude Children’s Research Hospital. He will be responsible for planning and managing the clinical staff, space and systems of the institution, to ensure the delivery of unsurpassed patient care to advance St. Jude’s mission. As an Executive Vice President, he will work with other members of the senior management team to provide overall administrative leadership of St. Jude.

Dr. Laver received his medical degree from the Technion Faculty of Medicine in Haifa, Israel, and a Master in Health Administration from the Medical University of South Carolina. His postdoctoral training includes a pediatric residency at the Assaf Harofeh Hospital in Zerifin, Israel, and a pediatric hematology/oncology fellowship and chief fellow in the Department of Pediatrics at Memorial Sloan-Kettering Cancer Center in New York. Dr. Laver also completed a pediatric research fellowship in the Laboratories of Developmental Hematopoiesis at Sloan-Kettering Institute in New York, NY. He is board-certified in Pediatrics and in Pediatric Hematology-Oncology. His areas of specialization include pediatric hematology/oncology and bone marrow transplantation. Dr. Laver was previously the Jesse Ball duPont Professor and Chairman of Pediatrics at Virginia Commonwealth University (VCU) Medical Center, and Medical Director of Children’s Hospital. He has served on the Board of Trustees of Children’s Hospital since joining VCU in 2000. Prior to his appointment as Chairman at VCU, he served as Vice Chairman of the Department of Pediatrics and Director of the Division of Hematology/Oncology and Pediatric Bone Marrow Transplantation Services at the Medical University of South Carolina.
St. Jude Clinical Trial Protocols

Below is a subset of clinical research protocols currently conducted at St. Jude. To find out more about the objectives of the studies below and their complete eligibility criteria, visit www.stjude.org/protocols, send an e-mail message to protocolinfo@stjude.org, or call the toll-free Physician Referral Line, 1-888-226-4343.

AML08: A Phase III randomized trial of clofarabine plus cytarabine versus conventional induction therapy and a Phase II study of natural killer cell transplantation in patients with newly diagnosed acute myeloid leukemia
- Eligibility: Patients less than or equal to 21 years of age with untreated acute myeloid leukemia.
- Principal Investigator: Jeffrey Rubnitz, MD, PhD

ANGI01: A Phase I study of bevacizumab and sunitinib combined with low dose cyclophosphamide
- Eligibility: Patients with a solid tumor or leukemia that has either come back (relapsed) or did not respond to treatment (refractory) or there is no therapy known to be effective.
- Principal Investigator: Fariba Navid, MD

OS2008: A study of bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), in combination with chemotherapy for treatment of osteosarcoma
- Eligibility: Patient must be newly diagnosed with high-grade, biopsy proven, osteosarcoma or malignant fibrous histiocytoma (MFH) of bone and should not have received prior chemotherapy or radiation.
- Principal Investigator: Najat Daw, MD

POCPZD: A Phase I study of the combination of ZD1839 (Iressa®) and irinotecan (Camptosar™) given orally in children with refractory solid tumors.
- Eligibility: Patients with a confirmed diagnosis of a recurrent solid tumor that did not respond to standard treatment or one for which there is no known therapy.
- Principal Investigator: Lisa McGregor, MD, PhD

SJHG04: A Phase I/II trial of a new tyrosine kinase inhibitor (tarceva; erlotinib hydrochloride; OSI-774) during and after radiotherapy
- Eligibility: Patients with newly diagnosed High Grade Glioma and Unfavorable Low-Grade Glioma
- Principal Investigator: Alberto Broniscer, MD

SJYC07: Risk-adapted therapy for children less than 3 with embryonal brain tumors, choroid plexus carcinoma or ependymoma.
- Eligibility: Patients under 3 with newly diagnosed medulloblastoma, supratentorial primitive neuroectodermal tumor (PNET), atypical teratoid/rhabdoid tumor (ATRT), choroid plexus carcinoma (CPC) or ependymoma
- Principal Investigator: Amar Gajjar, MD

BABYHU: A Phase III study of hydroxyurea vs. placebo on organ function in very young children with pediatric sickle cell anemia.
- Eligibility: Infants 9 to 12 months old with sickle cell genotype of Hb SS or Sβ0 thalassemia.
- Principal Investigator: Winfred Wang, MD

SWiTCH: A Phase III randomized clinical trial to compare standard therapy with alternative therapy for the prevention of secondary stroke and the management of iron overload in pediatric subjects with sickle cell anemia and previous stroke.
- Eligibility: Children with severe forms of sickle cell anemia between the age of 5 and 18.9 years.
- Principal Investigator: Russell Ware, MD

The Cure4Kids clinical education web site at St. Jude is continually adding new material to its seminar archives. Go to www.cure4kids.org and log in to take advantage of the numerous educational features and the digital library, as well as live conference rooms, working groups, and other networking features.

Adolescents and young adults with cancer: A new focus on a lost generation of patients, SIOP Keynote Lecture, Karen Albritton, MD

Medication-Induced Hematologic Toxicity, St. Jude Leukemia/Lymphoma Board, David Shook, MD, Jane S. Hankins, MD, MS, and Estela Ceja, PharmD

BRCA2 and Tumors of the Central Nervous System, St. Jude Solid Tumor Board, Mariko DeWire, MD, Robert P. Sanders, MD, Fred Laningham, MD, Melody J. Cunningham, MD, David W. Ellison, MD, PhD, MRCP (UK), FRCPath, and Peter McKinnon, PhD

Individualized therapy: in our lifetime? St. Jude Grand Rounds, Howard McLeod, PharmD

The Spleen: Function, Dysfunction, and Regeneration, St. Jude Leukemia/Lymphoma Board, Scott Maurer, MD and Jane S. Hankins, MD, MS

Overview of Acute Promyelocytic Leukemia (APL), St. Jude Leukemia/Lymphoma Board, Sara Federico, MD, Raul C. Ribeiro, MD, Susana Raimondi, PhD, and Sheila Shurtleff, PhD

Overview: Pediatric Bone Tumors, St. Jude Solid Tumor Board, Fariba Navid, MD

Biphenotypic Leukemias: Presentation, Treatment and St. Jude Experience, St. Jude Leukemia/Lymphoma Board, Giles Robinson, MD, Mihaela Onciu, MD, and Jeffery Rubnitz, MD, PhD
Although remarkable progress has been made in the treatment of children with cancer over the past 30 years, those with solid tumors such as high-risk neuroblastoma, anaplastic Wilms tumor, or alveolar rhabdomyosarcoma still have a very poor prognosis, despite multimodal treatment with increasingly aggressive chemoradiotherapy.1 Solid tumors are usually sensitive to cytotoxic chemotherapy initially, but they often develop into therapy-resistant disease to which children ultimately succumb. Clearly, new strategies for treating these patients are desperately needed. One such new approach is using angiogenesis inhibitors to target the tumor vasculature, thereby inhibiting tumor growth and metastasis.

**Angiogenesis inhibition**

Angiogenesis is the process of new blood vessel formation. In addition to being part of several normal physiologic processes, angiogenesis is an essential component of a number of pathologic conditions including cancer.2,3 Compelling data suggest that inhibiting angiogenesis not only can prevent tumor-associated neovascularization but also can impair tumor growth and spread.4,5 This approach to anticancer therapy is particularly appealing, because despite the extreme molecular and phenotypic heterogeneity of human cancer, most, if not all, tumor types most likely require neovascularization to achieve their full malignant phenotype. Therefore, antiangiogenic therapy may have a broad applicability for treating cancer, as well as the many other pathologic processes that depend on angiogenesis.

Angiogenesis inhibitors, often in combination with cytotoxic therapy, are now being introduced into pediatric solid tumor treatment plans. Numerous preclinical studies have focused primarily on models of adult tumors, and a number of recent clinical trials in adults have demonstrated antitumor synergy between angiogenesis inhibitors and cytotoxic agents. However, no rational or standardized guidelines defining the optimal scheduling and dosing of angiogenesis inhibitors have been established for treating children with solid tumors. At St. Jude, investigators in the Solid Malignancies Program are currently conducting comprehensive and integrated preclinical studies of the phenotypic and functional effects of angiogenesis inhibitors on tumor vasculature. Noninvasive imaging and pharmacokinetic and pharmacodynamic modeling in relevant models of pediatric solid tumors are being conducted. The results of these studies will be used to design clinical trials of angiogenesis inhibitors in children with solid tumors.

**Noninvasive assessment of the effectiveness of angiogenesis inhibitors**

The noninvasive assessment of the functional activity of angiogenesis inhibitors is key to ensuring their successful introduction into pediatric therapeutic protocols. However, the most appropriate imaging modality for children with solid tumors has not been determined. In adults, dynamic contrast-enhanced magnetic resonance imaging is widely used, but pediatric patients often require sedation or general anesthesia to undergo this type of examination. Another imaging modality, contrast-enhanced ultrasonography (CE-US), may be preferable because sedation is not required. This modality’s ability to assess the activity of angiogenesis inhibitors in pediatric solid tumors has not yet been tested; therefore, researchers at St. Jude have begun to evaluate the value of quantitative measurements of tumor contrast enhancement on CE-US images in orthotopic murine tumors treated with angiogenesis inhibitors.

In one study published in *Radiology*6, a team led by Beth McCarville, MD, Radiological Sciences and Andrew Davidoff, MD, Surgery, established retroperitoneal neuroblastomas in mice. From these studies, Davidoff’s group concluded that measuring intratumoral flow of an ultrasound contrast agent is a promising method for monitoring the vascular response of tumors to antiangiogenic therapy. Thus, they are continuing to evaluate the ability of CE-US and other noninvasive imaging methods to detect the effects of angiogenesis inhibitors on the vasculature of treated xenografts.

**Pharmacokinetic and pharmacodynamic modeling**

In addition to needing noninvasive ways to measure the efficacy of angiogenesis inhibitors, there is a need for comprehensive pharmacokinetic and pharmacodynamic modeling of the effects of angiogenesis inhibitors on the vasculature of treated xenografts.
to be produced in volumes larger than the typical 100-mL research scale and had to be created using the GMP facility’s 100-L bioreactor. The antibody-purification process also had to effectively remove any by-products from the cells used to produce the antibody. This process included challenging the antibody-purification process with known viral contaminants to illustrate the purification system’s ability to remove these viruses chemically and physically. The virology testing was performed off campus by a vendor who specializes in viral-clearance testing for clinical production. The off-site location also ensured that potential viral contaminants would not be introduced into the GMP facility.

FDA Approval Process

Detailed documentation of each step of the production process was required to demonstrate to the FDA that the process was controlled and reproducible. This documentation represents a significant part of the production process unique to the GMP facility. At several key purification steps, the antibody was analyzed using tests developed by the GMP’s Quality Control unit and the St. Jude Hartwell Center for Bioinformatics and Biotechnology to ensure that sufficient quantities of highly purified monoclonal antibody were being produced. “One of the biggest differences between research and production of clinical materials is the presence of a quality assurance group,” said Jim Allay, PhD, Director of Operations for the Children’s GMP, LLC. “They basically review that everything was done correctly and that the test results were reported correctly.” The investigation team petitioned the FDA for a preinvestigation of a new drug meeting before filing an IND (Investigational New Drug) application. The benefit of the petition was that the FDA personnel gave the GMP staff a great deal of feedback and some minor but crucial suggestions.

The Children’s GMP, LLC, Benefits St. Jude Research

“The nice thing about having the facility here at St. Jude is that if an investigator or a potential collaborator with a St. Jude investigator is interested in developing a therapeutic that he or she can not get a commercial partner to help produce, we have the capacity and the know-how to produce monoclonals, therapeutic proteins, and almost any other biological,” said Allay. Other members of the production team whose help was crucial in the process of manufacturing, purifying, and testing the antibody are Rob K. Clark, Scott Long, PhD, Robert Rutschman, and Mike Tillman all of the Children’s GMP, LLC.

Angiogenesis

Angiogenesis inhibitors, more preclinical data are needed to guide the dosing of antiangiogenic agents for children with solid tumors. Data from adult tumor models treated with these agents suggest that after treatment the tumor is temporarily more efficiently perfused, thereby potentially creating a window of increased access and effectiveness for adjuvant therapy with conventional cytotoxic agents. Davidoff’s team recently demonstrated that the angiogenesis inhibitor bevacizumab (Avastin™) has significant antitumor activity when combined with conventional cytotoxic chemotherapy in neuroblastoma xenograft models but that the timing of the dosing of the two agents is essential for achieving maximal antitumor efficacy.

Using a pharmacokinetic-pharmacodynamic approach rather than an empirical one is a more useful way to select the appropriate dosage schedule for translating preclinical antiangiogenic agent studies to the clinic. Once a pharmacokinetic model has been determined, optimal control methods can be used to determine treatment dosage and schedule under a given set of constraints. For example, investigators in the Solid Malignancies Program have already optimized topotecan dosing in children with high-risk neuroblastoma based on data from preclinical models. Results of their pharmacokinetic-pharmacodynamic modeling of that data suggest that protracted, low-dose topotecan treatment has a higher therapeutic index (i.e., more tumor killed with less toxicity) than the same total dose administered over a shorter period. By using pharmacokinetic and pharmacodynamic models, Davidoff and his colleague, Clinton Stewart, PharmD, Pharmaceutical Sciences, believe that they can translate the response to antiangiogenic agents (alone or in combination with cytotoxic agents) observed in preclinical studies into effective clinical trials for pediatric solid tumors.

Summary

Numerous preclinical studies and a few clinical trials in adults with solid tumors have shown that angiogenesis inhibitors are effective anticancer agents and that antitumor synergy exists between antiangiogenic agents and cytotoxic drugs. However, critical gaps in our understanding of how these agents work must be filled before they can be introduced into the multimodal therapy of pediatric solid malignancies. To address these issues, Davidoff, McCarville, and Stewart are using orthotopic pediatric xenografts to assess the ability of noninvasive imaging to accurately evaluate changes in tumor vasculature in response to antiangiogenic therapy, to determine the optimal
Ionizing radiation is an essential diagnostic tool for evaluating pediatric diseases, and its use in treatment management has become especially common with the increasing use of computed tomography (CT) imaging. CT use has increased annually by about 10% over the last 10 to 20 years, and more than 7 million pediatric CT examinations are done annually in the United States.2,3

The increased use of CT has triggered concerns over the safety of x-rays as reflected in recent reports of the potential risk of cancer from exposure to radiation during CT examinations. The conflicting opinions in the literature about the safety of CT scans for children have not obscured a consistent message—the estimated risk of a CT scan is far less than the benefit a patient derives from an indicated use of this imaging technique.1

**Measuring and Managing Risk**

The standard measure of ionizing radiation that takes into account the biological effects of this energy is the sievert (Sv), which is equivalent to 100 rads or 1 gray (Gy). For comparison, a dose less than 100 mSv is considered low-level radiation, and the average background radiation in the United States is 3 mSv/year per person. A typical radiation dose used for dental x-rays is 0.09 mSv, and a typical CT dose ranges from less than 1.0 to 30 mSv.

The cancer risk posed by a specific dose of radiation is greater in children than in adults for 3 reasons: 1) the growing tissues and organs of children are more sensitive to radiation effects than are fully mature organs; 2) the oncogenic effect of radiation can have a long latent period, so it has a longer time to manifest itself in a child than in an adult; and 3) radiation exposure from CT imaging usually results in a relatively higher dose for children because of their smaller cross-sectional body area compared to that of adults.3

This focus on the risk of CT imaging in particular is due to the relatively higher amount of exposure from this modality than from radiography, fluoroscopy, or angiography and the increasing number of indications for this type of imaging. Moreover, CT imaging can be done using a wide range of techniques and different radiation exposures that produce images of very similar quality. For example, until recently CT parameters at many institutions were the same for adults and children, but when pediatric doses were reduced by 50% to 90%, image quality remained satisfactory.1

Although the risk that irradiation poses to children remains of concern, no published studies have directly linked cancer to CT imaging. A study designed to determine such risk could require millions of patients. Nevertheless, recent consensus statements from the National Academy of Sciences (Biological Effects of Ionizing Radiation Committee), The United Nations Subcommittee on Atomic Radiation, and the International Commission on Radiation Protection provide guidance on this matter. Their statements suggest that it is reasonable to use CT imaging under the assumption that its low-level radiation poses a small risk of causing cancer. On the basis of this consensus, health care providers should incorporate 2 strategies for reducing that exposure:

- Use doses that are As Low As Reasonably Achievable (ALARA) and no more than required to acquire the necessary diagnostic information.
- Perform CT studies only when they are necessary.

Importantly, adult CT procedures commonly include multiple scans through the same body part, but most pediatric scans require only a single pass.

**Responsibilities of Clinicians**

The major responsibility of ensuring that children are exposed to a minimal amount of radiation rests with the pediatric health care professionals and radiologists. Pediatric health care professionals decide whether a CT is necessary and, therefore, must understand its risks and benefits and be able to discuss the risks frankly and clearly with patients and families. Pediatric health care professionals also should consult with the radiologist to determine whether CT is the optimal imaging modality for the child.

The responsibility of the radiologist is to perform CT examinations only when they are appropriate and to use techniques and radiation levels that are suitable for children. Radiologists must also stay current with rapidly evolving technologies.

**Using the ALARA (As Low As Reasonably Achievable) Approach Minimizes Radiation Exposure in Children**

**Responsibility of Pediatrician**

- Ensure the test is necessary
- Use the least invasive modality that has a high certainty of success
- Discuss case with radiologist to resolve any questions
- Understand radiation dose variations among different imaging modalities
- Base the procedure on medical indications, not on pressure from parents
- Share information with parents

**Responsibility of Radiologist**

- Review requests for higher-dose studies and perform them only when appropriate
- Discuss the case with the primary pediatrician
- Incorporate technical parameters that are suitable for children

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**Therapeutic Trends**

**ALARA Minimizes Ionizing Radiation Sequelae in Pediatric Patients**

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cont., p. 7
ALARA cont. from p. 6

For example, some new CT scanners can complete an infant chest examination in 1 second; future advances in CT design may better control radiation doses.

In summary, the benefits of CT scans substantially outweigh the risks. However, pediatric health care professionals and radiologists must understand how to extract the most information from the examination, while administering the minimal radiation dose to children. The byword for this cautious approach is ALARA. For more information about pediatric imaging, visit www.imagegently.org.

References

Angiogenesis cont. from p. 5

Timing and dosing of the combination of antiangiogenic and cytotoxic agents to achieve maximal antitumor efficacy and to devise a pharmacokinetic and pharmacodynamic model that will guide the dosing and scheduling of antiangiogenic agents for pediatric patients with solid malignancies.

References

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

CME credits will be available for selected educational seminars on Cure4Kids.org. For more information contact lindap.taylor@stjude.org.
You are called to evaluate a 12 hour old newborn male because the nurses have noted progressive tachycardia and poor oral intake over the past few hours.

The labor and delivery history was unremarkable and the baby’s physical examination was normal at birth (APGAR was 10 at 1 and 5 minutes).

On examination, the baby was normo-tensive and afebrile but had moderate tachycardia and tachypnea. There was evidence of central cyanosis but no cardiac murmur was heard.

The bedside ECG showed marked RVH and the CXR showed a small heart and pulmonary venous congestion.

**Question:** What is the name and significance of the abnormality in the RBCs listed below? What is the likely associated cardiac abnormality?

**Answer:**

The round dark RBC inclusion is called a Howell-Jolly Body and is associated with lack of appropriate spleen function. This newborn has congenital asplenia and it is important to recognize this early because he is at high risk of bacteremia and sepsis. In a newborn, congenital asplenia is associated with gram negative bacteria while in older infants and children, it is associated with pneumococcus. There is a strong clinical association between congenital asplenia and total anomalous pulmonary venous return (TAPVR).