2004

2003 Cancer Care Annual Report

Children's Mercy Hospital

2003

CANCER CARE

FOCUS ON AML

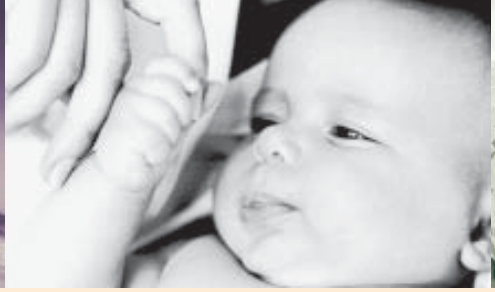
ANNUAL REPORT

Children's Mercy
HOSPITALS & CLINICS
www.childrens-mercy.org




Table of Contents



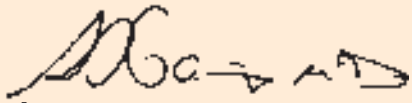



Letter *from* Director

Dear Colleagues,

The 2003 Children's Mercy Hospital Cancer Center Annual Report focuses on a cancer that extends across all ages of children and adults. Acute Myeloid Leukemia (AML) occurs in newborns, as well as the elderly. It is a cancer that both pediatric and adult oncologists struggle with on a daily basis. It remains one of the most difficult cancers to treat for children. Until the past decade, cure rates ranged from 20-25 percent. Today, cure rates have improved dramatically to almost 50 percent. However, AML carries the worst prognosis among all childhood cancers. As you will note in this report, therapy over time has evolved with success, but with great cost. In order to improve cure rates, therapy has become more intense and children who receive this treatment will experience prolonged periods of immune suppression. This places them at great risk for infection which is a leading cause of treatment-related mortality in the pediatric population. It's important to recognize, however, the significant advances in supportive care. Lessons from similarly immune suppressed patients, ie, those undergoing bone marrow transplant, show that protective environments, constant monitoring, and rapid initiation of antibiotics and evaluations will improve the survival of these children. In light of these facts, Children's Mercy Hospital constructed a specially designed patient care unit, 4 Henson, for all children undergoing chemotherapy. This unit utilizes the most advanced technology to protect children from infectious organisms in the environment, most notably fungi. Four (4) Henson is fully hepafiltered to reduce the risk of infectious complications for these children while still permitting them the freedom to leave their rooms. For all the children with cancer, this environment combined with multi-disciplinary care of the oncology care team provides a safe and comfortable place for them to be during their difficult therapy. This multi-disciplinary approach, outlined in this report, provides the expertise of many disciplines and specialties to provide a synergistic care that far exceeds the sum of its parts. This is the special aspect of the care received at Children's Mercy Hospital. We invite you to review the 2003 Annual Report which focuses on AML and illustrates the services and state-of-the-art care available for the children diagnosed with cancer in our region.

.



Alan S. Gamis, MD, MPH
Director of Oncology
Chair, CMH Cancer Care Committee




Letter *from* President/CEO

Dear Colleagues,

Children's Mercy Hospitals and Clinics continued its growth during the past year, with expansion of our facilities at both Children's Mercy Hospital in Kansas City and Children's Mercy South in Overland Park. We also opened a new location for specialty clinics and urgent care, Children's Mercy Northland, and all three locations continue to experience significant increases in the volume of patients seen and the range of services offered.

Our Division of Hematology/Oncology continued its growth and commitment to excellence during the past year, as well. Our program continues to be recognized by the American College of Surgeons as a national pediatric cancer center, and Children's Oncology Group, an NIH funded research consortium, recognizes Children's Mercy Hospital as one of the largest pediatric cancer centers in the country. In 2003, the cases of newly diagnosed oncology patients rose to 126, among the highest this program has seen.

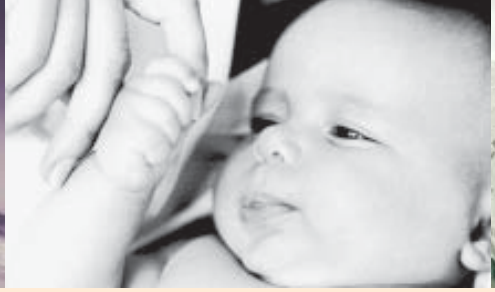
This 2003 Annual Report highlights Acute Myeloid Leukemia (AML), a more aggressive form of childhood leukemia which affects children of all ages. Approximately 800 new cases in children are diagnosed in the United States each year, with a median patient age of 4.5 years. Children diagnosed with AML continue to see poor survival rates and Children's Mercy Cancer Center is dedicated to seeing these rates improve through our collaborative efforts, also highlighted in this report.

We hope you will take a few moments to review our 2003 Cancer Center Annual Report to learn more about how we continue to dedicate ourselves to caring for children with cancer and their families and to finding new and better ways to provide treatments and cures.

Sincerely,

Randall L. O'Donnell, PhD
President & Chief Executive Officer






Division of Hematology/Oncology

The Division of Hematology/Oncology at Children's Mercy Hospitals and Clinics is dedicated to providing comprehensive care to children with cancer and blood disorders. Our goal is to provide this care in a family-centered care environment in an effort to promote health and well being. The division is divided into two sections: the Section of Oncology and the Section of Hematology. The Division Chair is Gerald Woods, MD. The Division Manager is Sue Stamm, RN, MHA, CPNP.

Family Centered Care Core Elements Supported by Division

- Respect the dynamics of the patient/family
- Acknowledge and empower the strength of the patient/family
- Provide choices to patients/ families, when available
- Provide unbiased and accurate information
- Provide emotional, financial, and spiritual support
- Provide flexibility
- Support a collaborative relationship between the patient/ family and the health care team.
- Empower the family to be a partner in the care of their child.

The Section of Oncology-Section Chief-Alan Gamis, MD:

- **The Bone Marrow Transplant Service-Interim Director-Alan Gamis, MD**: provides hematopoeitic stem cell rescue to patients receiving myelo-suppressive or ablative therapy which requires stem cell rescue. Stem cell rescue is accomplished by utilizing umbilical stem cells, matched-related donor cells, and matched-unrelated donor cells. There is a national Bone Marrow Transplant Consortium which is centered at Children's Mercy Hospital and the chairperson is Dr. Alan Gamis.
- **The Oncology Service-Director-Alan Gamis, MD**: dedicated to the treatment of malignant disorders. In 2003 this service diagnosed 126 new cases of cancer. The Oncology Service treats patients in accordance with clinical trials under the guidance of the Children's Oncology Group.

The Section of Hematology-Section Chief-Gerald Woods, MD

- **The Sickle Cell Disease Service-Service Director-Gerald Woods, MD**: offers specialized care for the unique diagnostic and treatment needs of children and adolescents diagnosed with sickle cell disease. These patients and families are confronted with episodes of acute pain, life limiting chronic pain, and other long term sequelae related to this devastating disease.
- **The Regional Hemophilia Center-Center Director-Brian Wicklund, MD**: supports seven sites in a five-state region to provide comprehensive treatment for both adult and pediatric patients with bleeding disorders. In addition, this service supports the diagnosis




Division of Hematology/Oncology

and treatment of coagulation and/or thrombosis disorders.

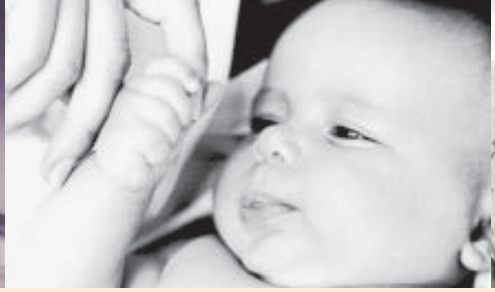
Children's Mercy Cancer Care Committee
The Children's Mercy Hospital Cancer Care Committee is a standing medical staff committee that provides oversight of the oncology services. The committee is chaired by the section chief for the Section of Oncology and has both physician and non-physician representation (see member listing). It is comprised of a multidisciplinary team of physicians, staff, and other discipline from across the institution. The committee meets quarterly and reviews patient acuity, program services and quality initiatives, and determines quality improvement needs and opportunities related to pediatric cancer prevention, diagnosis, treatment, and outreach. The committee functions in accordance with the American College of Surgeons' accreditation standards.

Pediatric Hematology/Oncology Fellowship Program
The fellowship program at Children's Mercy Hospital trains the future pediatric hematology/oncology specialists. This program requires intense clinical and research training for a minimum of three years. Each fellow at Children's Mercy Hospital enters the fellowship program as a fully trained pediatrician. The first 18 months are dedicated primarily to clinical care and becoming familiar with procedures and standards of practice. The subsequent 18 months are dedicated heavily to clinical and laboratory research. The Division of Hematology/Oncology at Children's Mercy Hospital currently supports three fellowship positions.

Case Management
Empowering.....is the goal of the nurses supporting case management in advanced practice or expanded nursing roles. The advanced practice/nurses in expanded roles include nurse practitioners, clinical nurse specialists, and nurse clinicians. The Bone Marrow Transplant Service utilizes two RN Program Coordinators for their case management. Each nurse is partnered with an attending MD to comprise a primary team for the children and family to identify. These nurses coordinate every aspect of the patient's care throughout treatment and during post-treatment follow-up. The case manager is the primary contact person for the patient and the family. Patient/family satisfaction was measured at several periods following the implementation of the case management model and satisfaction scores ranked high.

When the diagnosis of AML is confirmed, the case manager joins the physician in preparing and delivering a discussion with the family about the disease and the recommended plan for treatment. This information is repeated by the case manager through a series of individualized discussions, written educational material, handouts regarding the therapy plan, as well as, a Caregivers Oncology Handbook. The education, consultation and support given by the case manager at this crucial time ensures that the patient and family are well informed. Additional diagnostic and baseline studies, consultations and






Division of Hematology/Oncology

outside expert reviews, if indicated, are personally coordinated by the case manager.

Once the treatment plan has been established, the case manager walks through the phase of treatment or "roadmap", line by line with the patient and family members. Knowing what medications are due, what side effects may occur and how they will be monitored, strengthens the family's participation in their child's illness. The treatment plan is communicated to the staff who are directly involved with the child to ensure continuity of care both in and outpatient.

During therapy, the case manager oversees every aspect of the child's care. He/she provides written reminders about follow up appointments and lab work, clarify medications that may need to be administered at home, reiterate guidelines of when to seek medical care and when the child may attend school, church and social activities. The anticipatory guidance provided empowers the parents to resume their natural role with their child despite the AML, while meeting their own needs and that of their families and their employers. Those case managers practicing in advanced practice roles may also perform physical examinations, prescribe medications, and perform procedures within their credentialing privileges. The case manager is available by telephone and email to listen to the families concerns and answer their questions. Evening and weekend triage is provided by an advanced practice nurse and an oncology physician through our main hospital operator, 816-234-3000.

Throughout and following therapy, the child with AML may require multiple providers and services from a variety of disciplines and community agencies. The case manager can negotiate the various systems to gain the necessary services while assuring that the child does not get lost in the system. Insurance companies, home health agencies, and multiple other support and ancillary services are coordinated by the case manager while ensuring that the maximum coverage benefits are utilized. Ongoing contact with the referring pediatrician, the child's school and other providers ensures that those who participated with the child prior to the diagnosis of AML continue to be involved and informed throughout therapy. Despite the life-disrupting and life threatening nature of AML, families and children display remarkable resilience with the guidance, education and coordination provided by the case manager.

Physician's Assistants
Physician's Assistants (PA) are dedicated primarily to the Bone Marrow Transplant Service. Their role is supporting the day-to-day management of these patients, both inpatient and outpatient, in partnership with an attending MD. Program Coordinators work in close partnership with both the MD and PA to ensure the care is well coordinated.




Division of Hematology/Oncology

The Children's Mercy Cancer Center Cancer Care Conferences

The Children's Mercy Cancer Center Cancer Care Conferences provide opportunities for a multidisciplinary discussion regarding newly diagnosed patients, recurrent/relapsed patients, and unusual pediatric cancer cases. All patients diagnosed with a childhood cancer are discussed at these meetings. The conference consists of a review of the patient's history, physical findings at diagnosis, laboratory values, radiology exams, surgical interventions, and pathological findings. This diagnostic review is followed by a thorough review of the potential treatment options, current therapy available, response to therapy, if applicable, and anticipated prognosis. Medical specialists from oncology, surgery, pathology, radiology, radiation oncology, neurosurgery, orthopedic surgery, endocrine, psychology, and dentistry are represented. In addition, non-physician representatives include: advanced practice nursing, physician's assistants, hospital management/administration, social workers, child life specialists, chaplain, dieticians, and staff nurses. These cancer conferences are conducted in accordance with the American College of Surgeons' accreditation standards.

American College of Surgeons Requirements for Quality Assurance

Site Specific Studies for 2003

- AML-Oncology Services
- Neuroblastoma-Surgery Services

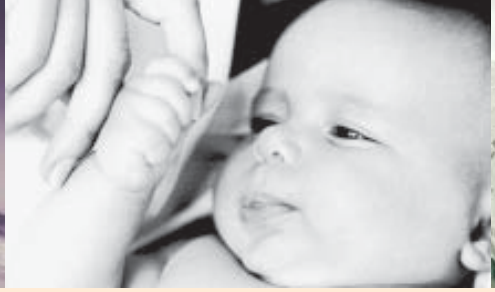
Quality Improvement for 2003

- Assessment of antibiotic therapy used for Fever and Neutropenia-Oncology Services
- Assessment of thoracoscopy for the diagnosis and treatment of malignancies-Surgery Services

Psychosocial Services

- **Parent-to-Parent Program:** designed to connect parents who have been through the cancer experience with parents of a newly diagnosed child with cancer. In addition, this program offers support groups on a weekly basis facilitated by parent volunteers under the oversight of a social worker.
- **Social Work and Community Services:** there are five full-time social workers dedicated to the Division of Hematology/Oncology. The primary focus of this team is to assist the patient and the family in understanding the impact the diagnosis of cancer will have on their family dynamics and life style.
- **Bereavement Support Group/Program:** this program is offered to parents who have experienced the loss of a child. The program includes staff contacts to parents/family members during significant events such as birthdays, anniversary date for the death of the child, an annual memorial service, and the composition of a memory book.






Division of Hematology/Oncology

- **Child Psychologist:** a full-time psychologist provides support to the patient, parents, and siblings of those diagnosed with childhood cancer.
- **Chaplaincy:** a full-time chaplain supports the spiritual needs of the patients and their families. There is a chaplain available 24 hours a day.
- **Child Life Therapist/Music Therapist:** two full-time Child Life therapists, one full-time Child Life assistant and one part-time music therapist work with patients, parents, and siblings to aid in the adjustment and ongoing support associated with diagnosis and treatment of childhood cancer.

Nutrition/Pharmacy Services

- **Nutrition:** two full-time and one part-time registered dietician support the nutrition needs of the patient/family. In addition, there is a nutrition tech that adds support to the team.
- **Pharmacy:** two full-time pharmacists and one full time technician support the operations of a satellite pharmacy Monday -Friday, 7:00 a.m. to 7:30 p.m. This satellite supports the inpatient and outpatient areas in preparing and dispensing chemotherapy. In addition, one full-time pharmacist provides clinical consultation to the oncology service and one full-time pharmacist provides clinical support to the Bone Marrow Transplant Service.

Cancer Outreach/School Re-entry Services

Participants: Nurse, Social Worker, Child Life Therapist/Music Therapist

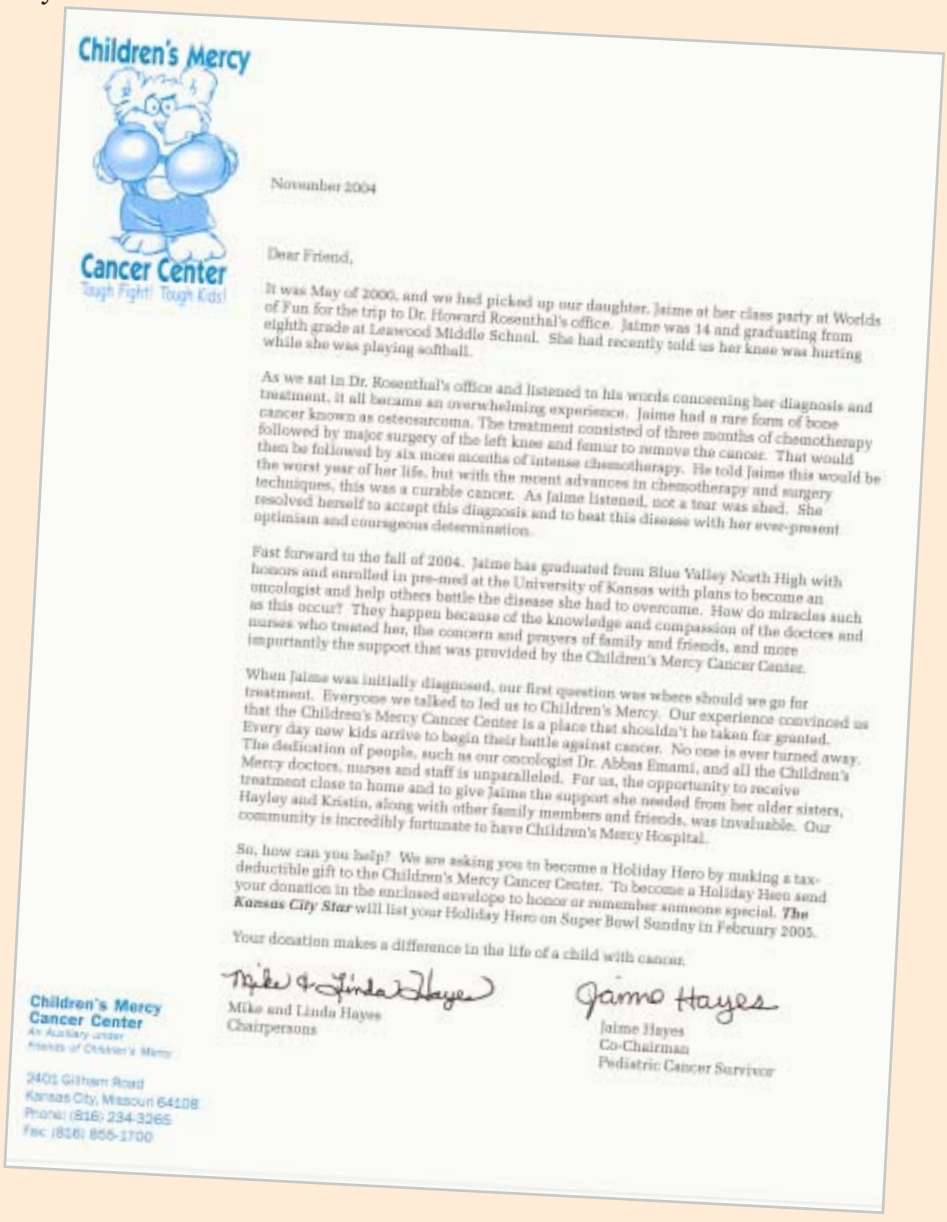
Goals/Objectives:

- Build a strong connection between hospital, parents/child, and the school.
- Identify hospital personnel as liaisons to the school.
- Provide school staff important information and allow them to ask questions which ultimately provides them with a better level of comfort/understanding while interfacing with the child and family.
- Peers "school mates" are given accurate information and area able to ask questions to relieve anxieties regarding cancer.
- Construct a support system through the school for the patient through peer comprehension and support.
- Provide an opportunity for preventive education/outreach regarding smoking cessation and sun exposure. These programs are tailored to the appropriate age group being spoken to.




Division of Hematology/Oncology

The Children's Mercy Cancer Center - Holiday Hero



Children's Mercy Cancer Center
Tough Fight! Tough Kids!

November 2004

Dear Friend,

It was May of 2000, and we had picked up our daughter, Jaime at her class party at Worlds of Fun for the trip to Dr. Howard Rosenthal's office. Jaime was 14 and graduating from eighth grade at Leawood Middle School. She had recently told us her knee was hurting while she was playing softball.

As we sat in Dr. Rosenthal's office and listened to his words concerning her diagnosis and treatment, it all became an overwhelming experience. Jaime had a rare form of bone cancer known as osteosarcoma. The treatment consisted of three months of chemotherapy followed by major surgery of the left knee and femur to remove the cancer. That would then be followed by six more months of intense chemotherapy. He told Jaime this would be the worst year of her life, but with the recent advances in chemotherapy and surgery techniques, this was a curable cancer. As Jaime listened, not a tear was shed. She resolved herself to accept this diagnosis and to beat this disease with her ever-present optimism and courageous determination.

Fast forward to the fall of 2004. Jaime has graduated from Blue Valley North High with honors and enrolled in pre-med at the University of Kansas with plans to become an oncologist and help others battle the disease she had to overcome. How do miracles such as this occur? They happen because of the knowledge and compassion of the doctors and nurses who treated her, the concern and prayers of family and friends, and more importantly the support that was provided by the Children's Mercy Cancer Center.

When Jaime was initially diagnosed, our first question was where should we go for treatment. Everyone we talked to led us to Children's Mercy. Our experience convinced us that the Children's Mercy Cancer Center is a place that shouldn't be taken for granted. Every day new kids arrive to begin their battle against cancer. No one is ever turned away. The dedication of people, such as our oncologist Dr. Abbas Emami, and all the Children's Mercy doctors, nurses and staff is unparalleled. For us, the opportunity to receive treatment close to home and to give Jaime the support she needed from her older sisters, Hayley and Kristin, along with other family members and friends, was invaluable. Our community is incredibly fortunate to have Children's Mercy Hospital.

So, how can you help? We are asking you to become a Holiday Hero by making a tax-deductible gift to the Children's Mercy Cancer Center. To become a Holiday Hero send your donation in the enclosed envelope to honor or remember someone special. ***The Kansas City Star*** will list your Holiday Hero on Super Bowl Sunday in February 2005.

Your donation makes a difference in the life of a child with cancer.

Mike and Linda Hayes
Chairpersons

Jaime Hayes
Co-Chairman
Pediatric Cancer Survivor

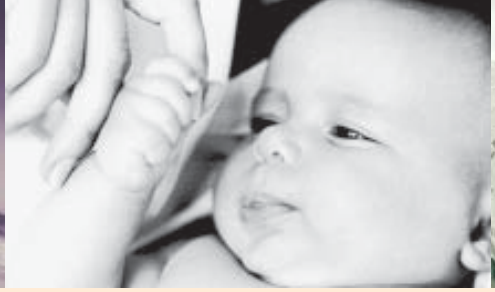
Children's Mercy Cancer Center
An Auxiliary under Friends of Children's Mercy

2401 Gillham Road
Kansas City, Missouri 64108
Phone: (816) 234-3265
Fax: (816) 855-1700

The Children's Mercy Cancer Center Web site offers patient/family education, as well as, public education regarding childhood cancer.

www.childrens-mercy.org






Cancer Care Board Members

MEDICAL STAFF MEMBERS

Andrews, Walter, MD	Surgery
Cooley, Linda, MD	Cytogenetics
Covitz-Hardy, Lynne, PhD	Developmental Medicine
Dalal, Jignesh, MD	Bone Marrow Transplant
Emami, Abbas, MD	Hematology/Oncology
Gamis, Alan S., MD-Chairman	Oncology/Bone Marrow Transplant
Gyves-Ray, Katherine, MD	Radiology
Hetherington, Maxine, MD-Assistant Chairman	Hematology/Oncology
Holcomb, G. Whit, MD	Surgery
Hornig, Gregory, MD	Neurosurgery
Huseman, Carol, MD	Endocrinology
Lewing, Karen, MD	Hematology/Oncology
Massey, Vickie, MD	Radiation Oncology
Modrcin, Ann, MD	Rehabilitation Medicine
Morello, Frank, MD	Radiology
Nicklaus, Pam, MD	Otorhinolaryngology
Sharp, Ronald, MD	Surgery-ACOS Liaison
Watanabe, Masayo, MD	Hematology/Oncology
Woods, Gerald, MD	Hematology/Oncology
Zwick, David, MD	Pathology

NON-PHYSICIAN MEMBERS

Bartholomew, Joy, RN, FNP, CPON	Hematology/Oncology
Baer, Phyllis, RN	Hematology/Oncology
Burns, Susan, RN, CPON	Hematology/Oncology
Corse, Cindy, CTR	Tumor Registry
Devorin, Barb, RN, CPNP	Neurosurgery
Fournier, Julie, RN, CPON	Hematology/Oncology-Clinic
Gonzalez, Celia, PA-C	Bone Marrow Transplant
Guevel, Wendy, RN, FNP	Surgery
Green, Nancy, Sr. CNS	Nutrition
Hutto, CJ, RN, MHA, CPON	Hospital Administration
Jones, Ronald, PA-C	Bone Marrow Transplant
Klockau,Chris, RPh, BCOP	Pharmacy
Laurence, Kris,	Hematology/Oncology
Marcus, Bette, RN, CPON	Hematology/Oncology
Mick, Kathy, RN, CPON	Hematology/Oncology
Ryan, Robin, CCRP	Hematology/Oncology
Seal, Annie, CLS	Child Life
Stegenga, Kristin, RN, PCNS, CPON	Hematology/Oncology
Von Fange, Jill, LAASW, MSW	Hematology/Oncology
Walter, Christy, LPN	Hematology/Oncology

Cancer Registry

The Cancer Registry is a vital part of the Cancer Care Program at Children's Mercy Hospital. This year's statistics reflect the highest number of patients ever to enter the registry with a total of 126 patients. From January, 1990 through December, 2003 the Cancer Registry has recorded 1,237 patients. The registry at CMH contributes to cancer surveillance and control by the following methods:

- Collecting and maintaining data on all types of malignancies.
  - Data collected include: patient demographics, cancer type and location, stage of disease at diagnosis, treatment received, recurrence and follow-up information.
- Collecting data on certain benign/ borderline conditions as approved by the Cancer Care Committee. These conditions are monitored because of location or propensity to recur and/ or progress to malignancy. (see Figure 2)
- Assigning a Class of Case according to the criteria set forth by the American College of Surgeon (ACOS). This data item shows the role that CMH plays in the patients diagnosis and treatment. (see Figure 2)
- Providing data to the Missouri Central Cancer Registry, the National Cancer Data Base, and physicians. This data is essential in the epidemiological study of cancer incidence, survival, and treatment effects on a local, state and national level.
- Following our cancer patients annually throughout their lifetime to check on their health status.
- Participating in the approval process for our facilities accreditation from the American College of Surgeons Commission of Cancer. The Children's Mercy Cancer Program was awarded full three-year approval at the last survey in July 2002.

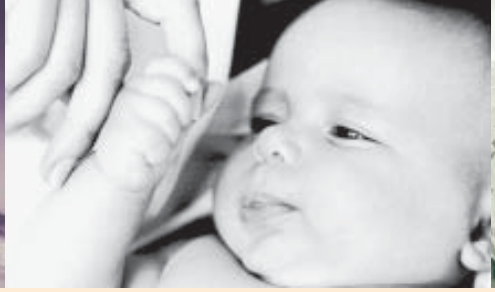
The most frequent diagnoses during 2003 were tumors of the central nervous system representing 31 percent of the annual caseload. There were 28 diagnoses of leukemia making up 22 percent of the 2003 patients. (see Figures 1 and 4)

The geographical area of the 2003 patients coming to CMH for cancer care included 42 different counties from three states. Of those, there were 20 Missouri counties, 19 Kansas counties and one Nebraska county represented. (see Figure 5)

The most frequent diagnoses during 2003 were tumors of the central nervous system...

Twenty-one cancer-related deaths were reported in 2003, seven of which were diagnosed the same year, and most of which were identified as tumors of the central nervous system. (see Figure 3)






Cancer Registry

Children's Mercy Hospital Cancer Registry 2003 Frequency of Diagnosis
FIGURE 1

Central Nervous System	**39**	**(31%)**
Astrocytoma	11	
Medulloblastoma	5	
Glioma	4	
Atypical Teratoid/ Rhabdoid Tumor	3	
Ependymoma	3	
Glioblastoma Multiforme	2	
Germinoma	1	
NG Germ Cell Tumor	1	
Benign/Borderline Tumors	9	
Leukemia	**28**	**(22%)**
ALL	23	
AML	5	
Lymphoma	**8**	**(6%)**
Non-Hodgkins	4	
Hodgkins	4	
Neuroblastoma	**12**	**(10%)**
Osteosarcoma	**7**	**(6%)**
Ewings Sarcoma	**4**	**(3%)**
Wilms	**3**	**(2%)**
Other	**25**	**(20%)**
Retinoblastoma	2	
Rhabdomyosarcoma	1	
Hepatocellular Carcinoma	1	
Renal Cell Carcinoma	1	
Adenocarcinoma	1	
Pleuropulmonaryblastoma	1	
Clear Cell Sarcoma	1	
Malignant Rhabdoid Tumor	1	
Fibrosarcoma	1	
Undifferentiated Sarcoma	1	
Misc. Reportable Conditions	14	

Class of Case (ACOS-COC Classification) and Reportable Conditions
FIGURE 2

Class 0 = 0 (0%)
Diagnosed at CMH – received all of first course of treatment elsewhere.

Class 1 = 84 (67%)
Diagnosed at CMH – received all or part of first course of treatment at CMH.

Class 2 = 16 (13%)
Diagnosed elsewhere – received all or part of first course of treatment at CMH.

Class 3 = 4 (3%)
Diagnosed elsewhere – received all of first course of treatment elsewhere. Now at CMH with recurrence, disease progression, or subsequent treatment.

Reportable Conditions*
(Benign / Borderline) = 22 (17%)
Included in the Registry due to location of tumor or because of its propensity to recur.

**The Cancer Care Committee has approved the following conditions to be included in the Registry. These conditions are collected in addition to the histologic malignant behavior cases.*

- Borderline / Benign lesions of the Central Nervous System
- Mesoblastic nephroma
- Teratomas, regardless of locations
- Theca cell- granulosa cell tumor
- Lymphoproliferative Disease
- Ganglioneuroma
- Myeloproliferative Disease
- Langerhan's Cell Histiocytosis

Cancer Registry

2003 Mortality Data
Figure 3

Central Nervous System		**7**
Medulloblastoma	1	
Ependymoma	2	
Glioblastoma Multiforme	1	
Atypical Teratoid/ Rhabdoid Tumor	2	
Brain Stem Glioma	1	
Leukemia		**5**
ALL	1	
AML	3	
Juvenile Myelomonocytic Leukemia	1	
Rhabdomyosarcoma		**2**
Neuroblastoma		**2**
Ewings Sarcoma		**1**
Osteosarcoma		**1**
Malignant Rhabdoid Tumor		**1**
Lymphoepithelial Carcinoma		**1**
Myeloproliferative Disorder		**1**
Total Number of Mortalities in 2003		**21**

AML Patients
5 Year Survival Comparison Rate

SEER 5-YEAR RELATIVE SURVIVAL RATES (PERCENT)
AGES 0-19* - 1995-2000 = 49.5%

CMH 5- YEAR KAPLAN-MEIER ADJUSTED SURVIVAL RATES
(PERCENT) AGES 0-20** - 1994-2003 = 47.5%

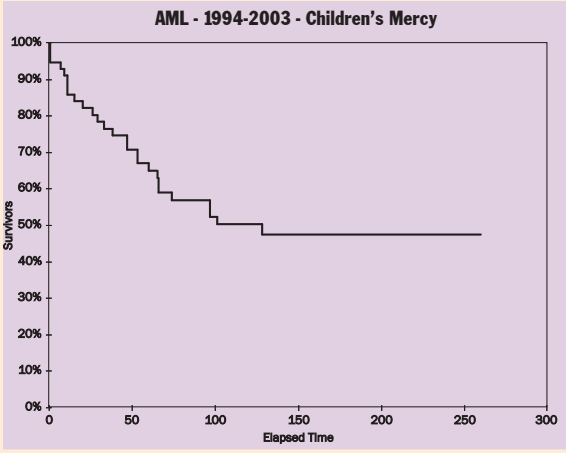
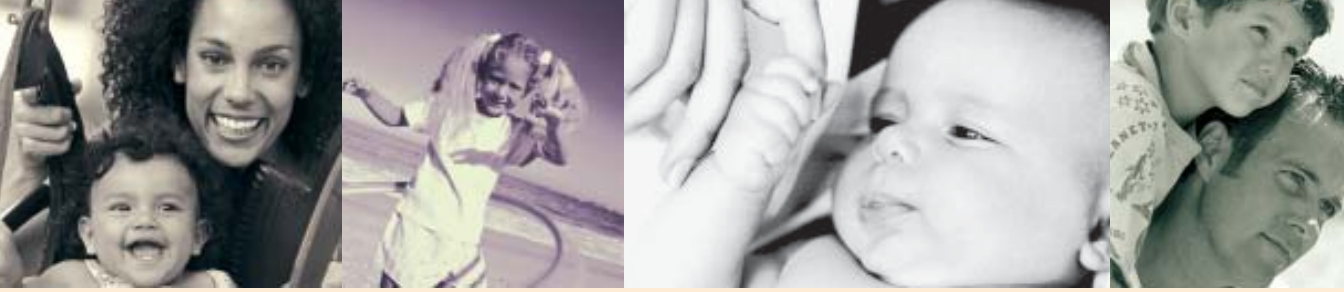


**Table XXVII-8 SEER Cancer Statistics Review 1975-2000*
*** Cancer Registry Management: Principles and Practice- Pg 431 comparison of Relative and Kaplan-Meier Adjusted Survival Modules*

AML: Age and Sex Distribution-10 Year Comparison

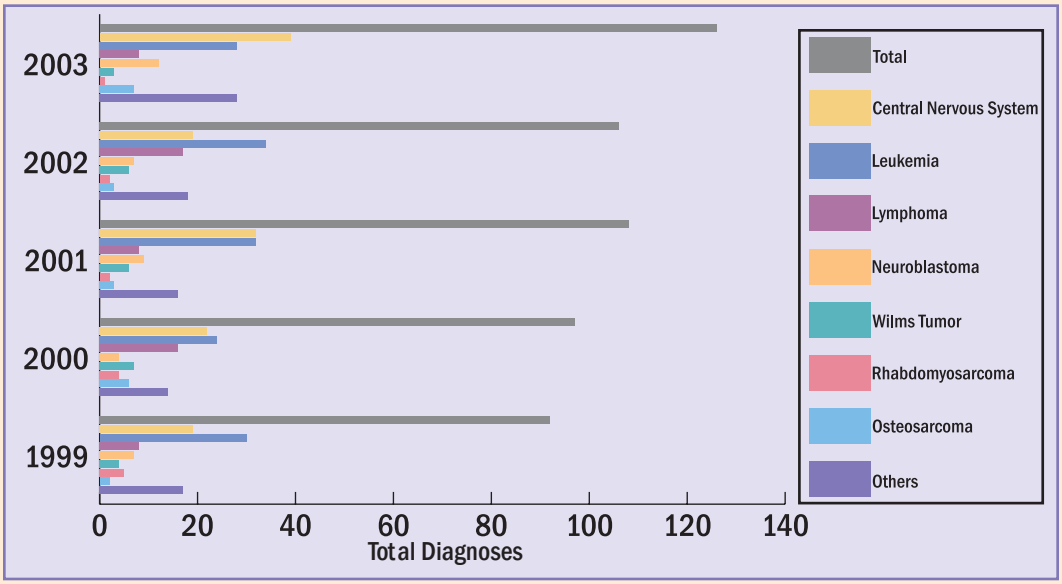
YEAR	TOTAL	MALE	FEMALE	AGE 0-2	AGE 3-6	AGE 7-10	AGE 11-16	AGE >16
2003	5	4	1	0	1	0	4	0
2002	10	5	5	5	2	1	2	0
2001	6	3	3	2	0	2	1	1
2000	5	2	3	2	0	1	1	1
1999	6	4	2	1	3	1	1	0
1998	8	5	3	1	3	1	3	0
1997	3	0	3	0	1	0	2	0
1996	5	0	5	2	1	1	0	1
1995	5	3	2	1	0	1	2	1
1994	4	2	2	1	2	0	1	0
TOTAL	**57**	**28**	**29**	**15**	**13**	**8**	**17**	**4**



CANCER REGISTRY

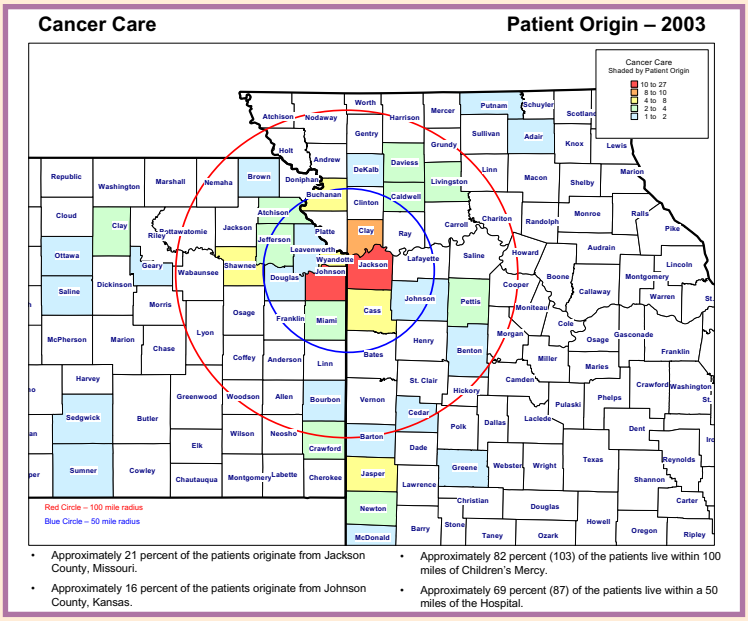
A FIVE-YEAR COMPARISON OF MOST FREQUENTLY OCCURRING DIAGNOSES AT CHILDREN'S MERCY HOSPITAL

FIGURE 4



CANCER CARE MAP - PATIENT ORIGIN

FIGURE 5



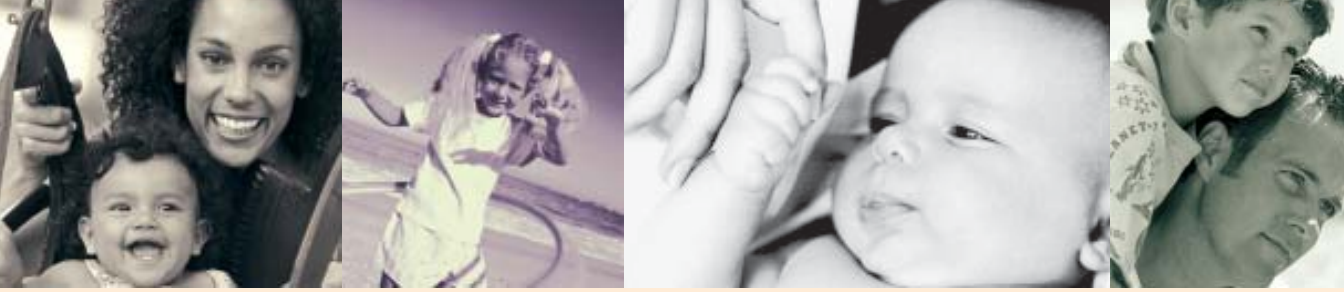
Acute Myeloid Leukemia

Leukemia is a malignant disease of the blood-forming organ, the bone marrow. Hallmarks of a cancer cell include a proliferation and survival advantage over normal cells, impaired differentiation into a mature cell, and the capacity for endless self-renewal. Acute myeloid leukemia (AML) results from an uncontrolled proliferation and maturation block in the granulocytic or myeloid series of cells. AML is also known by the synonymous terms: acute myelogenous leukemia, acute myelocytic leukemia, acute non-lymphocytic leukemia (ANLL) and acute myeloblastic leukemia. AML accounts for ~15-20 percent of all leukemia in childhood, while acute lymphoblastic leukemia accounts for ~75 percent-80 percent. It has a relatively high frequency in infancy (10 per million children) and thereafter occurs at a relatively constant frequency (5-10 per million) into adolescence after which its incidence increases to where in adulthood, it is the predominant form of acute leukemia. In general, there is a 1/14,000 risk of developing AML in childhood. Most patients do not have a recognized genetic predisposition for the development of leukemia. However, rare heritable disorders known to predispose children to leukemia include Fanconi anemia, Bloom syndrome, ataxia telangiectasia, Kostmann syndrome, and others. Individuals with Down syndrome are 14-20 times more likely to develop acute leukemia than children in the general population. While, after age 5 years, the overall ratio of AML to ALL is the same for DS children as for children in the general population, before 5 years of age AML is 46x more common in the DS child. In addition to this increased incidence of leukemia, newborns with Down syndrome may show a transient myeloproliferative disorder (TMD) that is clinically indistinguishable from leukemia. In contrast to true leukemia, the TMD usually spontaneously regresses within one to two months. Some of these children (30 percent) will later develop true leukemia.

Acute myeloid leukemias are classified by the morphologic characteristics of the cells and by genetic abnormalities. The FAB classification shown in Table 1 classifies subtypes of AML by cell

TABLE 1

French American and British (FAB) Classification	Enzyme Reaction Pattern in Blasts		
FAB Subtypes	MPO	Butyrate	Chloroacetate ES
• M0 undifferentiated	-	-	-
• M1 Minimally differentiated	+	-	+(-)
• M2 Differentiated	+	-	+
• M3 Promyelocytic	+	-	-(+)
• M4 Myelomonocytic	+	+	+
• M4eo Myelomoncytic w/ abnormal eosinophils	+	+	+
• M5 Monocytic / monoblastic	-(+)	++	-
• M6 Erythrocytic	+	-	-
• M7 Megakaryocytic	-	-(+)	-



Acute Myeloid Leukemia

differentiation, immunohistochemical staining characteristics, and lineage of the cell, e.g., granulocytic, monocytic, erthryocytic, megakaryocytic.

Table 2 lists the most common recurrent chromosomal and genetic abnormalities and their clinical significance. Cytogenetics at the time of diagnosis is widely recognized as one of the most important prognostic determinants in AML. Approximately 75-80 percent of cases show clonal chromosome abnormalities at diagnosis. Correlation of chromosome abnormality with overall survival and event free survival finds a favorable prognostic impact for patients with inv(16)/t(16;16), t(8;21), t(15;17), and t(9;11). Unfavorable cytogenetic abnormalities include monosomy 7, other 11q23 abnormalities, and other rare recurrent translocations. All other abnormalities and a normal karyotype are included in an intermediate prognostic group, e.g., +8, +21. (Figure 1) Not only do these identify prognosis, but they also identify the etiologies of the leukemia. By

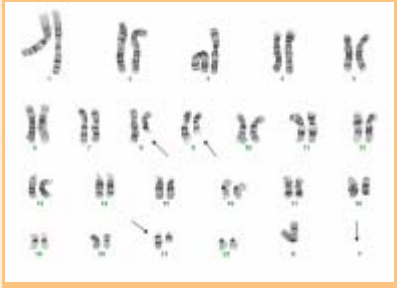


Figure 1 - 45,X,-Y,t(8;21)(q22;q22),del(9)(q22q34) Favorable prognosis karyotype.

TABLE 2
RECURRENT CHROMOSOME ABNORMALITIES IN CHILDHOOD MYELOID DISORDERS

Chromosome Abnormality	Genes Involved	FAB Subtype	Incidence	Prognosis	Comment
t(8;21)(q22;q22)	ETO/AML1	AML-M2	10-15%	Good	Older age, males, extramedullary tumors
t(15;17)(q22;q21)	PML/RARA	AML-M3	10-12%	Good	Older age, responsive to ATRA
inv(16)/t(16;16)	CBFB/MYH11	AML-M4eo	6-10%	Good	Increased risk of CNS disease/relapse
t(11q23;v)*	MLL	AML-M4/M5	10-13%	Poor	Infants, high WCC, CNS & skin disease
		t-AML		Poor	Epipodophyllotoxin exposure
t(9;11)(p22;q23)	AF9/MLL	AML-M5a	~5%	Good	Clinically indistinguishable from other MLL rearrangement
t(1;22)(p13;q13)	OTT/MAL	AML-M7	<1%	Poor	Infants
-7		AML	4-7%	Poor	
-7 / 7q-		1° MDS	50-60%	Poor	7q- often found in complex karyotype
-7 / 7q-		t-AML	5-7%	Poor	Alkylating agent exposure
-7		Aplastic anemia	1-2%	Poor	Risk of transformation to leukemia
-7		JMML	6-24%		Young age, favorable with BMT
+8		AML	5-10%	Intermed	Often with other chromosome abnormalities

FAB, French-American-British (classification); AML acute myelocytic leukemia; t-AML therapy-related AML; ATRA all-trans retinoic acid;
MDS myelodysplastic syndrome; AA aplastic anemia; JMML juvenile myelomonocytic leukemia; CNS central nervous system;
WCC white cell count
*All translocations involving 11q23, MLL gene rearrangement with chromosomes other that chromosome 9

Acute Myeloid Leukemia

placement of genes in abnormal locations by translocation or the elimination of normal genes by deletion, the normal control mechanisms of cellular proliferation are missing which in turn results in the uncontrolled proliferation of the cells, or leukemia.

Of the clonal chromosome abnormalities detected at diagnosis, ~55-60 percent are the recognized recurrent abnormalities mentioned. The majority of these abnormalities may also be detected using a molecular cytogenetic method, fluorescence in situ hybridization (FISH). This method utilizes DNA probes for the specific abnormality or translocation under investigation. For patients with one of these abnormalities detected at diagnosis, FISH is utilized for post-therapy and post transplantation monitoring of disease status. (Figures 2 and 3)

Secondary AML in children previously treated for other types of malignant disease is rare, but of increasing concern due to the high cure rate and long life expectancy for children with cancer. Chromosome abnormalities associated with previous treatment include monosomy 7, 7q deletion, t(8;21), inv(16), 11q23, and 21q22 abnormalities. Chromosome 11q23 abnormalities are associated with exposure to the epipodophyllotoxins such as etoposide (VP16) and chromosome 7 abnormalities are associated with exposure to alkylating agents. A recent study correlated the risk of epipodophyllotoxin-related AML with the schedule of drug administration and not with the cumulative drug dose. Patients with secondary AML whose cells show the t(8;21) or inv(16) fare better than patients with -7, 7q-, 11q23 and 21q22 abnormalities.

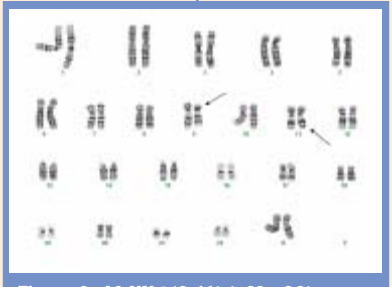


Figure 2. 46,XX,t(9;11)(p22;q23) Favorable prognosis karyotype.

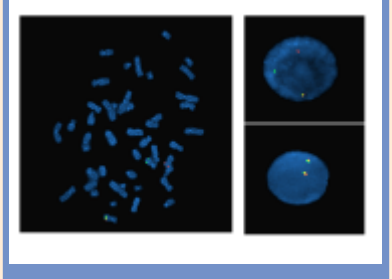
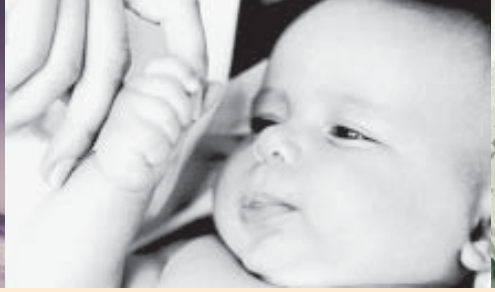


Figure 3. FISH with MLL gene probe; located on chromosome 11 at band q23. Left metaphase picture shows a red/ green signal on the normal chromosome 11, a green signal on the abnormal chromosome 11, and a red signal on the abnormal chromosome 9. This signal pattern confirms the t(9;11) seen in the karyotype in Figure 2 interrupts the MLL gene. Upper right shows the same interruption of the MLL gene in an interphase nucleus with the red and green signals separated. The lower right shows two normal MLL gene signals. Interphase nuclei are used to assess presence of the clone following therapy or transplantation.

Myelodysplastic syndrome (MDS), a clonal disorder characterized by ineffective hematopoiesis, morphologic abnormalities, and relatively low percentages of blasts, is rare in childhood with an annual incidence of 4 per million. The FAB classification of MDS comprises five






Acute Myeloid Leukemia

subgroups: RA, RARS, RAEB, RAEB in transformation, and pediatric JMML. A new classification system (WHO) has redefined acute myeloid leukemia as a myeloid neoplasia with 20 or more percent blasts in the marrow, thereby eliminating the RAEB-T subgroup. Loss of chromosome 7, either as monosomy 7 or deletion 7q, is the most common cytogenetic abnormality in childhood MDS. Monosomy 7 or 7q deletion occurs in 30 percent of children with MDS and ~5 percent of children with AML. Monosomy 7 as the sole chromosome abnormality was associated with an overall 3-year survival of 56 percent in patients with MDS compared with a 3-year OS of 13 percent in those with AML. For most children with MDS, ie, those with RAEB ±T, therapy is identical to those with AML.

A successful outcome, ie, cure, for children with AML continues to be a difficult challenge with an overall long-term survival only recently approaching 50 percent (note among all children with cancer, there is a combined cure rate now in excess of 70 percent). This however, is a 100 percent improvement over cure rates of the 1980's which were at best 20-25 percent. This has come from collaborative efforts of organizations, such as the National Cancer Institute's Children's Oncology Group of which Children's Mercy Hospital is a major institution among over 230 programs. COG is the largest childhood cancer program in the world. Complete remission is achieved in >70-80 percent of children with AML after one or two courses of chemotherapy, but approximately half of these patients have occult disease that can lead to relapse. Remission and cure is achieved only through intensive therapy that is only exceeded in toxicity by bone marrow transplantation. For this reason, children undergoing therapy for AML must remain hospitalized for weeks at a time, extending from each of their chemotherapy administrations until their white blood counts recover. Through this extreme caution, treatment related mortality (TRM) rates throughout North America have fallen by half, from approximately 15 percent to now 7 percent. Therapy typically consists of 4-5 intensive courses of therapy extending over approximately 6-8 months depending upon the time it takes each child to recover from each course. Clinical trials performed in the 1990's from COG, and on which children from CMH participated, showed that utilization of a bone marrow transplant from an HLA matched sibling conveyed a 10-15 percent improved survival rate. For the 20-25 percent of children who have this option, it is typically performed after 2-4 cycles of chemotherapy. As of yet, for those without a sibling donor, the increased TRM that comes with unrelated donor transplant or a mismatched related donor transplant exceeds any improvement in relapse rates. These types of transplants are reserved for those who relapse and in whom cure without transplant is rare.

Careful monitoring of the response to chemotherapy allows the caregiver to further determine / refine prognosis and subsequently to tailor therapy to the individual patient. Follow-up bone

Acute Myeloid Leukemia

marrow morphological examination assesses treatment response and evaluates the percentage of leukemic blasts remaining in the marrow. The burden of disease as evaluated by morphologic examination 7, 14, and 28 days after induction therapy correlates with outcome. Cytogenetic and FISH studies assess the presence or absence of any clonal chromosome abnormality detected at diagnosis. For those patients with abnormalities detectable by molecular DNA probes, FISH is a highly sensitive (0.5 percent) method for detecting low levels of residual disease. FISH is particularly helpful in patients who have undergone an opposite sex donor transplantation. In addition to assessing engraftment status with sex chromosome DNA probes, the sex chromosome probes can be combined with probes specific for the diagnostic clone to detect very low levels (0.001-0.00005) of residual disease in host cells (Figures 4 and 5). These newer techniques, performed at CMH, allow better-tailored regimens to the patient's needs. Additional methods are under study including multiparameter flow cytometry and PCR studies for such markers as Flt3-ITD, both of which in early study have been significant prognostic indicators.

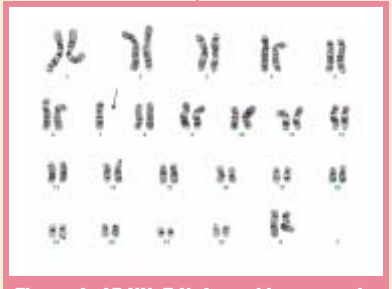


Figure 4. 45,XX,-7 Unfavorable prognosis karyotype.

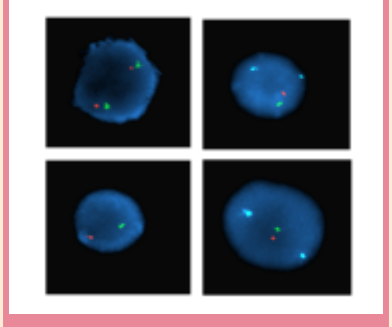
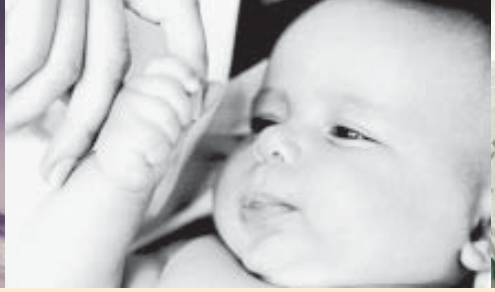


Figure 5. FISH using probes for the X chromosome (aqua) and chromosome 7 centromere (green) and chromosome 7 long arm (red). The upper left shows a nucleus with two normal chromosomes 7; lower left shows a nucleus with one chromosome 7 (monosomy 7), the upper and lower right shows two nuclei with two chromosomes X and one chromosome 7 (female cells with monosomy 7). This method detects host cells with the clonal abnormality after opposite sex donor transplantation.

Advances in therapy for children with cancer show that we are truly on the threshold of a new millennium. Two of these advances are the use of monoclonal antibodies and the use of protein or kinase inhibitors. Monoclonal antibodies, based upon techniques that identified that leukemia cells have unique surface markers that can serve as targets for antibodies that are designed to carry chemotherapy agents directly to the cancer cell. This therapy, now at the phase where it is to be fully tested in children to determine whether it truly improves cure rates, offers a new approach to our traditional methods of giving chemotherapy that go to all cells in our body (but fortunately affect cancer cells more adversely). This trial, to be performed in the COG, is being led by Children's Mercy investigators. Subsequent to the full






Acute Myeloid Leukemia

mapping of the human genome, researchers (such as those at Children's Mercy including Peter Rogan, PhD, who is close to identifying the gene that confers the higher risk of leukemia upon children with Down Syndrome) are now leading the field toward the use of new agents that are more specific and safer. These agents are aimed at the abnormal proteins (kinases) that are created by the genetic mistakes that are found in cancer cells. In Chronic Myelogenous Leukemia (CML), imatinib, the first agent in this new class of drugs has dramatically changed the face of therapy, taking a disease that was only curable with bone marrow transplant, to a disease that can be placed in full remission by the use of this single agent without any of the side effects seen with traditional chemotherapy. These agents are uniquely developed for each type of genetic mistake. For each cancer, there may be dozens of different mistakes that can occur that lead to the same cancer, as is seen in AML. For AML, several specific agents are under study in the earliest phases of human testing, ie, to first determine their safety before being fully tested. It is anticipated that as further discoveries are made in better understanding the genetic mistakes that create cancers, there will be further development of agents in this new class of drugs that will revolutionize the care and the cure of childhood AML. However, until that time occurs which may still be more than a decade away, we continue to work to improve cure rates for our young patients with AML, either through better traditional agents or through better techniques of reducing complications.

Children's Mercy researchers are highly active in the search for better cures in childhood AML, either through the reduction in side effects or with the use of newer techniques and agents. The following is a sample of the recent and current work underway by these investigators.

National Clinical & Laboratory AML Trials with a CMH Investigator*

Children's Cancer Group CCG-2951: Acute Myeloid Leukemia Salvage Therapy for Patients in First Relapse or Who Fail to Achieve an Initial Remission or Who Develop Acute Myeloid Leukemia as a Second Malignant Neoplasm

Children's Cancer Group CCG-B957: Localization of genes predisposing to acute leukemia in Down Syndrome

Children's Oncology Group COG-A2971: Treatment of Children with Down's Syndrome and AML, MDS, and Transient Myeloproliferative Disorder

Children's Cancer Group CCG-E23: Children with Down Syndrome <19yrs Newly Diagnosed with Leukemia between 1/1/97 and 12/31/01

Children's Oncology Group COG-AAML0431: The Treatment of Down Syndrome Children with Acute Myeloid Leukemia and'Myelodysplastic Syndrome under the Age of 4 Years

Acute Myeloid Leukemia

Children's Oncology Group COG-AAML0531: Phase III Randomized Trial of Gemtuzumab Combined with Conventional Chemotherapy for de novo Acute Myeloid Leukemia in Children

[*] *Either as a study chair or as a study committee member.*

CMH AML Publications

PK **Rogan**, P Close, JL Blouin, JR Seip, L Gannutz, RL Ladda, and SE Antonarakis (1995) **Duplication and loss of chromosome 21 in two children with Down syndrome and acute leukemia.** Am J Med Genet 59(2): 174-81.

PK **Rogan**, DW Sabol, and HH Punnett. (1999) **Maternal uniparental disomy of chromosome 21 in a normal child.** Am J Med Genet, Mar 1999; 83(1): 69-71.

Gamis A, Howell B, DeSwarte J, Feusner J, Woods W. (2000) "Incidence and impact of alpha streptococcal infections in a prospective childhood AML trial, CCG 2891 - A report from the Childrens Cancer Group", Journal of Clinical Oncology, 18:1845-1855.

Sandler ES, Hagg R, Mustafa MM, Gamis A, Kamani N, Wall D. (2000) "Hematopoietic stem cell transplantation with a conditioning regimen of busulfan, cyclophosphamide and etoposide for children with acute myelogenous leukemia (AML): A phase I study of the Pediatric Blood and Marrow Transplant Consortium", Medical and Pediatric Oncology, 35(4):403-409.

Gamis A, Hilden J. (2002) "Transient Myeloproliferative Disorder A Disorder with too little Data and many Unanswered Questions: Does It Contain an Important Piece of the Puzzle to Understanding Hematopoiesis and AML?" J Ped Hemat Oncol, 24(1):2-5.

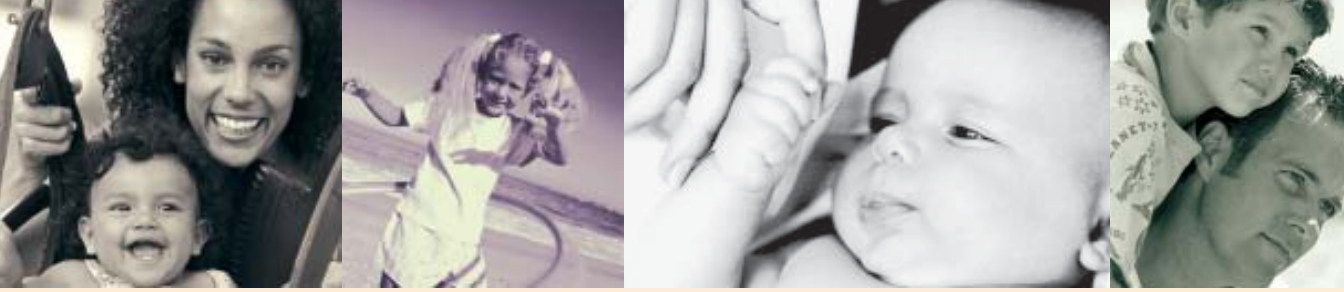
Mundshau G, Gurbuxani S, Gamis A, Green M, Arceci R, Crispino J. (2003) "Mutagenesis of GATA1 is an initiating event in Down syndrome leukemogenesis", Blood, 101(11): 4298-4300. Pre-published Online – Jan 30, 2003.

Gamis A, Woods W, Alonzo T, Buxton A, Lange B, Barnard D, Gold S, Smith F (2003) "Increased Age at Diagnosis Has a Significantly Negative Effect on Outcome in Children with Down Syndrome and Acute Myeloid Leukemia—A Report from the Children's Cancer Group Study, CCG-2891", Journal of Clinical Oncology, 21(18):3415-3422, prepublished online – Aug 1, 2003.

Wells, R, Adams M, Alonzo T, Arceci R, Buckley J, Buxton A, Dusenbery K, Gamis A, Masterson M, Vik T, Warkentin P, Whitlock J. (2003) "Mitoxantrone and Cytarabine Induction, High Dose Cytarabine and Etoposide Intensification for Pediatric Patients with Relapsed or Refractory Acute Myeloid Leukemia: Children's Cancer Group Study 2951", Journal of Clinical Oncology, 21(15):2940-47.

Greene M, Mundshau G, Wechsler J, McDevitt M, Gamis A, Karp J, Gurbuxani S, Arceci R, Crispino J. (2003) "Mutations in *GATA1* in both Transient Myeloproliferative Disorder and Acute Megakaryoblastic Leukemia of Down syndrome", Blood Cells, Molecules, and Diseases, 31(3):351-6.

Gamis A. (2005) "Acute Myeloid Leukemia and Down Syndrome – Evolution of Modern Therapy, State of the Art Review", Pediatric Blood & Cancer, 44(1): 13-20, prepublished online – Aug 24, 2004.



References

Marinez-Climent JA and Garcia-Conde J. Chromosomal rearrangements in childhood AML and MDSs. J Pediatric Hem/Oncol 21(2):91-102, 1999.

Rubnitz, JE, etal. Favorable impact of the t(9;11) in childhood AML. J Clin Oncol 20(9):2302-2309, 2002.

Raimondi SC, etal. Chromosomal abnormalities in 478 children with AML: Clinical characteristics an treatment outcome in a cooperative Pediatric Oncology Group Study-POG 8821. Bllod 94(11):3707-3716, 1999.

Grimwade D, etal. The importance of diagnostic cytogenetics on outcome in AML: Analysis of 1,612 patients entered into the MRC AML10 trial. Blood 92(7):2322-2333, 1998.

Wells RJ, etal. Prognostic variables in newly diagnosed children and adolescents with AML: Children's Cancer Group Study 213. Leukemia 16:601-607, 2002.

Mrozek K, etal. Cytogenetics in acute leukemia. Blood Reviews 18:115-136, 2004.

Pui C, etal. AML in children treated with epipodophyllotoxins for ALL. NEJM 325:1682-1687, 1991.

Haslw H, etal. Myelodysplastic syndrome, juvenile myelomonocytic leukemia, and AML associated with complete or partial monosomy 7. Leukemia 13:376-385, 1999.

Luna-Fineman S, etal. Childhood monosomy 7: epidemiology, biology, and mechanistic implications. Blood 85(8):1985-1999, 1995.

Smith MA et al, Leukemia, in Ries LAG et al (eds), Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995, National Cancer Institute, SEER program. NIH Pub. No. 99-4649, Bethesda, MD, 1999.

Lange B. The management of neoplastic disorders of haematopoiesis in children with Down's syndrome. Br J Hematol 110:512, 2000.

Woods W et al. A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute
myeloid leukemia in remission: a report from the Children's Cancer Group. Blood 97:56, 2001.

Vardiman J et al. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 100:2292, 2002.

Children's Mercy Hospitals and Clinics
2401 Gillham Road
Kansas City, Missouri 64108
816-234-3000
www.childrens-mercy.org

Credits

Joy Bartholomew, RN, MSN, FNP, CPON - Contributing Editor • *Linda Cooley, MD* - Contributing Editor/Editor
Cindy Corse, CTR - Contributing Editor • *Alan Gamis, MD* - Contributing Editor • *Telisa Hassen* - Editor/Designer
CJ Hutto, RN, MHA, CPON - Contributing Editor/Editor • *Robin Ryan, CCRP* - Contributing Editor