

Pediatric ALL & Program Update

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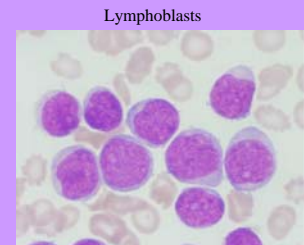
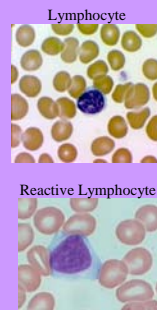
Case

- 14 yo boy with 3 day history of sore throat, fever to 102°, and cervical lymphadenopathy is seen in a local ED
- He is given steroids for “mono”
- The next day her mom brings him to the ED because he’s been throwing up all day and can’t keep anything down

Case

- CBC showed WBC 1,200 w/ majority of cells blasts, H/H 6.9/19.5, & plts 33

Peripheral blood blast morphology



Case

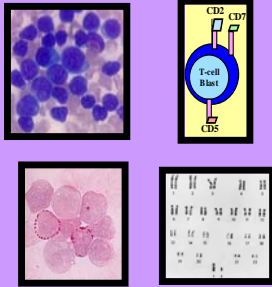
- CMP with K 4.6, uric acid 7.7 (nl), phos 6.0 (nl), BUN 9, Creat 0.8
- LDH 5574
- PT & PTT nl, Fibrinogen 216, D-dimer neg
- Blood culture done d/t fever

Case

- Patient admitted to PICU
 - Broad spectrum antibiotics d/t fever
 - Hydration, allopurinol to prevent tumor lysis syndrome
 - CXR done to r/o mediastinal mass
 - EKG, echo done as baseline
 - Titers for VZV, CMV, & HSV
- Time for diagnostic procedures!

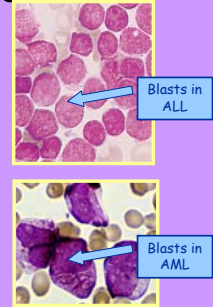
Diagnostic Workup: Bone Marrow Analysis

- Morphology
- Cytochemistry
- Immunophenotyping
- Cytogenetics

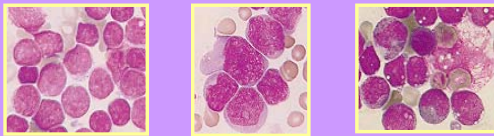


Bone Marrow Analysis: Morphology

- Description of leukemic cells
 - Size, shape, amount of cytoplasm
 - Other characteristics (e.g., vacuoles, Auer rods)
- Cells classified according to the FAB (French-American-British) system
 - ALL: FAB L1 – L3
 - AML: FAB M0 – M7



Morphology in ALL: FAB Classification



L 1

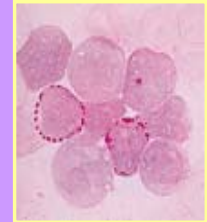
L 2

L 3



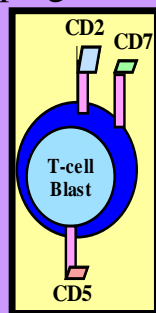
Bone Marrow Analysis: Cytochemistry

- Special stains applied to slides
- Helps to differentiate cell lineage (AML: Sudan black, myeloperoxidase versus ALL: periodic acid-Schiff/PAS)
- Helps to differentiate AML subtypes



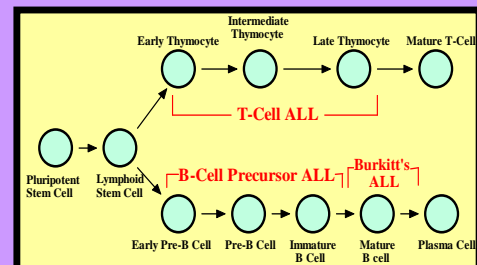
Bone Marrow Analysis: Immunophenotyping

- Identifies markers (antigens) on blast cells
- Helps to differentiate:
 - ALL vs. AML
 - T vs. B lineage ALL
 - Certain subtypes of AML



Types of ALL

Pre-B cell (84%) T-cell (15%) B-cell (1%)

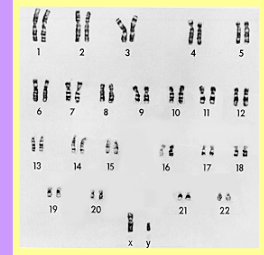


Subtypes of ALL

- **Precursor-B Cell**
 - Most common type
 - Commonly seen in preschoolers
- **T-Cell**
 - Associated with high WBC
 - Often associated with mediastinal mass
 - Commonly seen in adolescent males
- **Mature B-Cell (Burkitt's)**
 - Responds poorly to standard ALL therapy
 - Treatment same as for Burkitt's lymphoma

Bone Marrow Analysis: Cytogenetics

- Analysis of leukemic cell chromosomes
- Chromosome number (ploidy)
- Chromosome structure
 - Deletions
 - Translocations



Cytogenetics in ALL: Ploidy

- **Ploidy** = number of chromosomes
 - **Normal** – diploid (46)
 - **Hyperdiploid** – extra copies of chromosomes (usually favorable)
 - **Hypodiploid** – missing copies of chromosomes (always unfavorable)



Cytogenetics in ALL: Structural Changes

Type	Associated Gene Product	Prognostic Implication
t(12;21)	TEL-AML1	Favorable
t(4;11)	MLL	Unfavorable
t(9;22)	BCR/ABL (Philadelphia Chromosome)	Unfavorable
Trisomy 4, 10, 17	None	Favorable

Diagnostic Workup: Lumbar Puncture

- Standard component of workup for acute leukemia
- Cell count & cytospin done
 - CNS 1: WBC < 5 & no blasts on cytospin
 - CNS 2: WBC < 5 w/ blasts on cytospin
 - CNS 3: WBC > 5 w/ blasts on cytospin
 - Results in cranial XRT, augmented therapy
- Initial intrathecal chemotherapy often administered during diagnostic tap to take advantage of sedation (not in Seattle)



Case

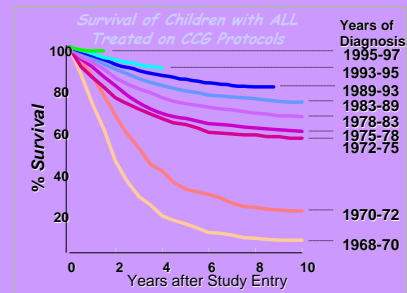
- Bone marrow shows a predominance of pre-B cell lymphoblasts & CSF has 3 WBC and no blasts noted on cytospin (0 RBCs)
- Our patient is enrolled on the COG Classification Study

Clinical Trials in Pediatric Oncology

- Childhood cancer is rare
- Most pediatric oncology clinical trials are conducted in cooperative groups
- Cooperative groups provide for:
 - Increased patient accrual
 - Collaboration among institutions
 - Rapid progress
 - Improved treatments



Impact of Cooperative Group Trials

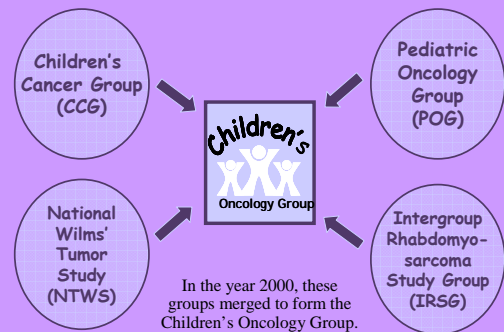


The Pediatric Cooperative Groups



Over last half of 20th century, four major pediatric oncology clinical trials groups emerged.

The Cooperative Group Merger



Children's Oncology Group

- More than 200 member institutions
 - United States/Canada
 - Switzerland/The Netherlands
 - Australia/New Zealand
- More than 5000 individual members
- About 5000 patients/year entered on clinical trials
- About 35,000 survivors now in active follow-up
- Multidisciplinary meetings 2x/year
- Member website with on-line access to protocols



Cooperative Clinical Trials: Interdisciplinary Focus



- Pediatric Oncology
- Radiation Oncology
- Surgical Oncology
- Nursing
- Bioethics
- Pathology
- Clinical Research Associates
- Stem Cell Transplant
- Biology and Translational Research
- Epidemiology
- Late Effects
- Psychology
- Pharmacology
- Patient Advocates

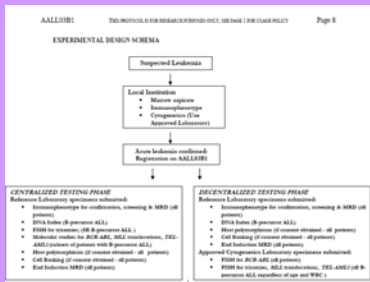
Patient Access to Clinical Trials

- Pediatric oncology clinical trials
 - Designed for specialized population
 - Usually available only through tertiary care centers or their affiliates
- All children and adolescents with cancer need access to clinical trials
 - Proven survival advantage for participants
 - Improved treatments benefit all patients

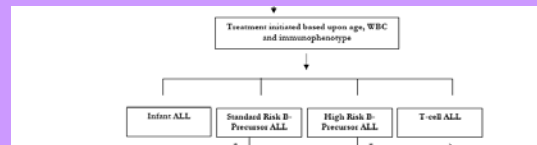
Patient Access to Clinical Trials

- Institution must be a COG member in order to enroll patients on COG trials
- Institutional membership requires a laundry list of personnel, availability of services, and the enrollment of a certain number of children per year
- Currently, TCHAP is not a member of COG so in order for our patients to have access to COG trials, every child travels to Seattle Children's at the time of diagnosis.

COG ALL Classification Study



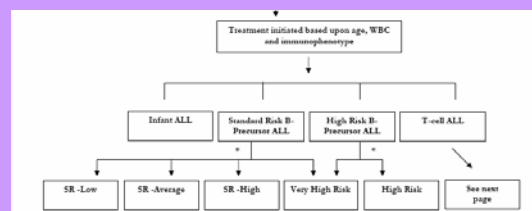
COG ALL Classification Study



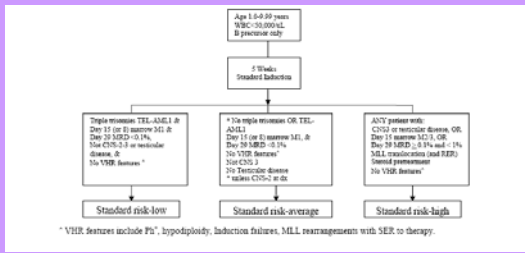
NCI classification system of ALL

	Standard Risk	High Risk
Age	1-9.999 yrs	≥10 yrs
WBC	<50,000	≥50,000
Steroid pre-treatment	No	Yes

COG ALL Classification Study



Classification of SR ALL



Since it will take 4 weeks to have all the information necessary To determine SR-Low vs. Ave. vs. High vs. Very High risk, There is a common induction chemo regimen for all SR ALL

SR ALL Induction

- “Three drug therapy” lasting 5 weeks
 - Vincristine IV push weekly
 - Dexamethasone orally daily
 - Asparaginase IM
 - (Intrathecal methotrexate & Ara-C)
- Current open study extends induction x 2 weeks for patients who are not in remission (<5% blasts in marrow) at day 29

ALL Induction

- Technically “easy” drugs to administer
- Highest mortality from infection is during induction so need good support for fever evaluations, infections, etc.

Faster response to therapy portends a more favorable prognosis

- Bone Marrows done at day 8, day 15, & day 29 of induction
- If remission (<5% blasts) by day 15, this means the patient is a rapid early responder (RER) and has a better prognosis
- If remission not achieved by day 15, pt is a slow early responder (SER)
- Latest COG study is also looking at the presence of MRD (>0.1% detectable blasts by flow cytometry at day 29)

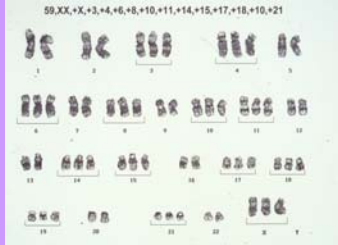
Case

- Our patient completes induction
- 98% of ALL patients will be in remission at the end of induction
 - Defined as less than 5% blasts in bone marrow and count recovery from initial chemo
- What information have we learned in the first four weeks to tell us about our patient’s prognosis?

Case

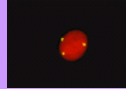
- Bone Marrow day 8 showed 20% blasts (not remission)
- Bone Marrow day 15 showed < 5% blasts (**remission**)
- Bone Marrow day 29 showed < 5% blasts (**remission**) with no blasts detectable by flow cytometry
- Patient is a **rapid early responder**

Cytogenetics

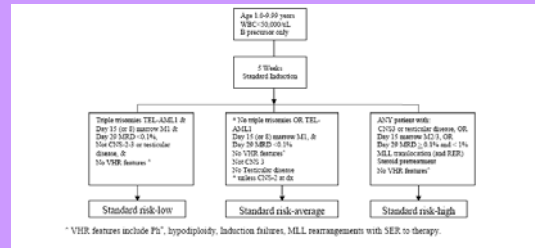


Cytogenetic analysis done on blasts at diagnosis shows trisomies (3 copies) of chromosomes 4, 10, & 17 (“Triple trisomies”)

“FISH”



Classification of SR ALL



Our patient qualifies as standard risk – low!

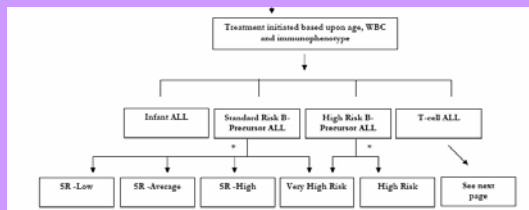
SR ALL chemotherapy

- Induction – **very intense**
- Consolidation – start PCP prophylaxis
- Interim Maintenance
- Delayed Intensification – **intense**
- Maintenance

Current COG SR ALL Study

- SR Average
 - Randomization b/t standard & intensified consolidation
 - Randomization b/t standard & augmented IM & DI
- SR High
 - Non-randomly assigned to intensified consolidation, augmented IM & DI, and double DI
 - XRT for CNS3 (>5 WBC & + blasts) or testicular disease

COG ALL Classification Study



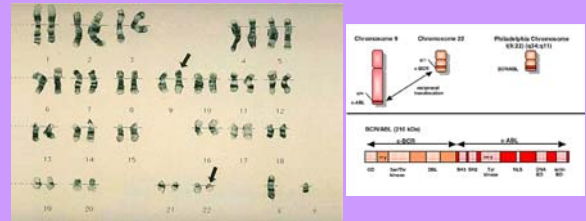
HR ALL

- “Four drug induction”
 - Vincristine
 - Steroid
 - Asparaginase
 - Daunorubicin (anthracycline)
- Current study is randomization b/t prednisone & dexamethasone in induction and “Capizzi” IV methotrexate & “high dose” methotrexate during IM
- SERs, MLL rearrangements, and CNS/testicular dz non-randomly assigned to most intense + extra DI

Very High Risk ALL

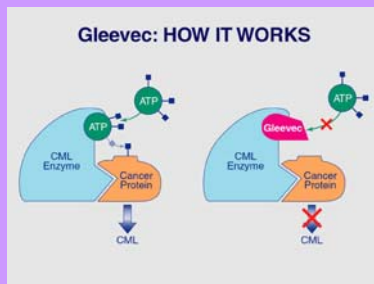
- Philadelphia chromosome (+), hypodiploidy, and MLL rearrangement w/ SER are eligible
- Very intense chemo and cranial XRT w/ HSCT for those with matched sib \pm gleevec for Philadelphia chromosome (+)
- Prognosis is poor

Philadelphia Chromosome



Translocation seen in CML (>95%) and ALL (4%)

Gleevec



T-cell ALL

- Make up 15% of childhood ALL
- Slightly worse prognosis (EFS 85%) than B-cell ALL
- Current study stratifies patients according to response to therapy and tests high dose methotrexate & Nelarabine (nucleoside analogue) in the treatment of T-cell ALL
- All but low risk get cranial XRT

Infant ALL

- Patients diagnosed less than one year of age are eligible
- EFS 35-40%
- Commonly associated w/ 11q23 (MLL gene) rearrangement
 - Same genetic defect in leukemia post- etoposide chemotherapy
 - Signs of leukemia retrospectively found in NBS samples
 - ? In utero exposure to carcinogen
- Treated aggressively, often including bone marrow transplant



Long term follow-up



- Rapidly expanding field made more important (and possible) by a growing number of childhood cancer survivors



Off-therapy ALL care

- Patients need to come to clinic monthly in the first year off therapy for follow-up CBCs & physical exams
- PCP prophylaxis may be discontinued 3 months after stopping therapy
- Subsequent years visits will become less frequent
- “Cure” is defined as remission 5 yrs off therapy

Long term complications from therapy for ALL

- Literature is fairly depressing
 - Cohort of longest term survivors treated in an era when cranial XRT given prophylactically to all kids with ALL
 - Craniospinal XRT affects pituitary function, growth, pubertal development, neurocognitive function, dentition

Long term toxicity of ALL treatment

- Fertility not affected (unless receive BMT)
- Cardiotoxicity from anthracyclines
 - Rare w/ ALL cumulative doses
- Osteoporosis, AVN, & “metabolic syndrome” from steroids
- Secondary malignancies rare (esp. w/o CNS XRT) but dreaded complication

Long Term Outlook for ALL

- Quality of life generally good for most survivors
- Probably a lot fewer complications in patients treated on newer protocols
- We’re nearing (or at) the end of our ability to improve survival using conventional chemo
- The future is in molecularly targeted therapies

Program Update

Requirements for Quality Pediatric Oncology Program

1. Opportunity for patients to participate in cooperative group clinical trial.
2. Protocol driven therapy using best available therapies and supportive care.
3. Capability of appropriately handling diagnostic tumor tissue (surgical, pathology, processing, send out). Note: eligibility for clinical trials increasingly requires sending properly processed tumor specimens to central lab.
4. Chemotherapy delivery process, to include roadmaps, roadmap revision, order writing, co-signature, pharmacy process, nursing process, quality improvement process.

Requirements for Quality Pediatric Oncology Program

5. Supportive care process (standard procedures, child life, social work, nutrition, housing).
6. Twenty-four hour availability of knowledgeable providers, familiar with process and with care guidelines. Assurance of prompt evaluation and management complications of chemotherapy (fever and neutropenia, need for transfusions, etc.)
7. Process of communication and decision-making that assures multidisciplinary, multi-institutional care of complex cancer patients.

Requirements for Quality Pediatric Oncology Program

8. Appropriate triage of patients based on prospectively agreed upon criteria: diagnosis, stage, complexity, risk and treatment capabilities.
9. Stable defined program leadership with shared vision and responsibility for program oversight, quality improvement, inter-institutional decision making.

The Challenge:

Cancer rate: For each 1,000,000 children less than 20 years old, 150 per year are diagnosed with cancer.

There are 199,000 children less than 20 years old in Alaska, therefore we should expect 29 new diagnoses per year.

In 2008, 30 cases/year and 2018, 34 cases per year.

50% is outside Anchorage metropolitan area

Alaskan Pediatric Cancer Burden

- In calendar year 2006
 - 20 new diagnosis cancer patients (may not include Southeast)
 - 6 ALL, 3 AML, 3 Brain tumors, 2 Hodgkin's disease, 2 NHL, and one each of Wilms tumor, colon cancer, Ewing's sarcoma and neuroblastoma
- At Providence in 2006
 - 17 oncology patients in active treatment
 - 3 Native Alaskans
 - 4 post-transplant on immune suppression

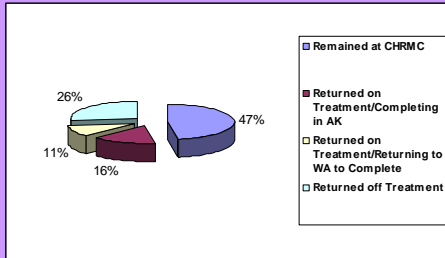
AK patients referral pattern to Seattle CHRMC

- Of 20 new diagnosis patients in 2006
 - 17 evaluated at PAMC at time of diagnosis
 - 2 went through ANMC w/ Dr. Schulz consulting
 - 1 sent to CHRMC by PCP w/o Dr. Schulz' involvement
 - 18 total sent to CHRMC (1 deceased, 1 required no further treatment after tumor resection)

AK patients transitioning back from Seattle CHRMC

- Of 18 patients sent to CHRMC in 2006
 - 9 returned to Alaska since diagnosis
 - Ave. time in Seattle 3.5 mos (range 1-6.5 mos.)
 - 4 returned off therapy
 - 5 returned on therapy
 - 2 ALL who are returning to Seattle for DI
 - Remaining 3 kids have or will finish out therapy at PAMC
 - » One each Wilms tumor, NHL, and colon cancer

AK Patients transitioning back from Seattle CHRMC



Current level of oncology care at TCHAP

- All new diagnosis patients transferred to Seattle CHRMC for access to COG trials (proven improved survival with clinical trial access in many pediatric cancers)
- Patients return home when TCHAP able to provide the level of care required for remainder of therapy (exception ALL interim maintenance)

Current level of oncology care at TCHAP

- TCHAP chemo administered in 2006 for
 - ALL interim maintenance & maintenance
 - Lymphoblastic lymphoma maintenance
 - Emergent induction for T-cell lymphoblastic lymphoma d/t patient too unstable for transport
 - Histiocytosis
 - EBV lymphoproliferative disease
 - Wilm's tumor

Next step for program

- Administration of “delayed intensification” for lymphoblastic leukemias and lymphomas
 - Approx. 12 hrs of hydration & chemo infusion once during cycle requiring inpatient chemo capabilities
 - Need for good care of pediatric neutropenic fever

Questions?