Hematology/Oncology Pharmacy Association 2009

Significant Papers in Pediatric Oncology: Phase I Studies – Current Status and Future Directions

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Disclosure

- Susannah E. Koontz, PharmD, BCOP has received consulting fees from sanofi-aventis and fees for non-CE services from Enzon Pharmaceuticals, Genzyme Oncology, and sanofi-aventis. She is also an IRB member for Pediatric Central IRB (NIH/NCI)

Learning Objectives

- Identify key Phase I pediatric oncology studies published in the medical literature within the past 16 months
- Cite historical challenges to conducting Phase I trials in pediatric patients with cancer
- Discuss the future evolution of Phase I trials in pediatric oncology patients

Warm-Up Question

?

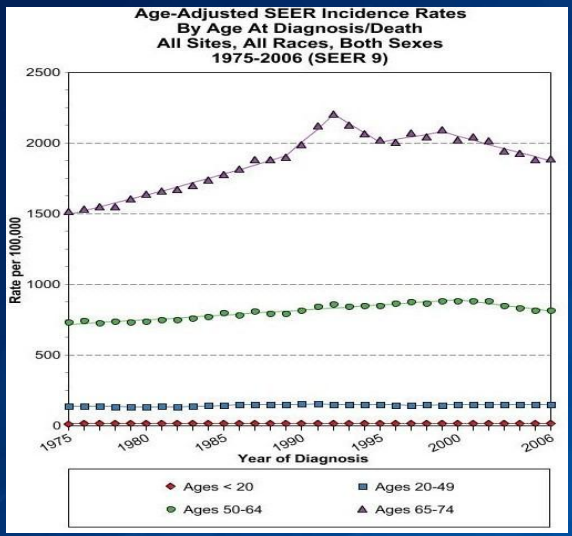
- Between January 2008 and April 2009, approximately how many Phase I studies conducted in pediatric patients (< 21 years old) were reported in the primary medical literature?
  - A.) < 15
  - B.) 15 – 30
  - C.) 30 – 45
  - D.) > 45

Looking at Novel Therapeutics

- Two publications addressing the need for new therapeutics for pediatric cancers
  - "How Do We Identify Novel Treatment for Childhood Cancer?"
    - Commentary on a Phase II study by Peter J. Houghton
  - "Clinical Drug Development for Childhood Cancers"
    - News & Views by Frank M. Balis, et al

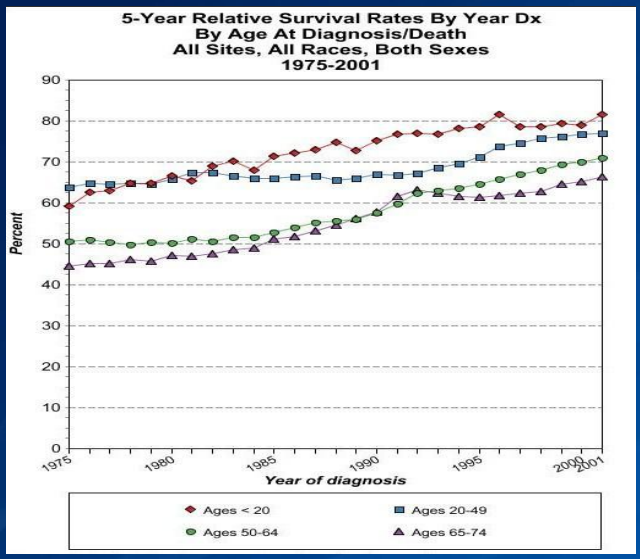
Houghton PJ. *Pediatr Blood Cancer.* 2009;52:310-1.
Balis FM, et al. *Clin Pharmacol Ther.* 2009;85:127-9.

Cancer Incidence Rates in the US



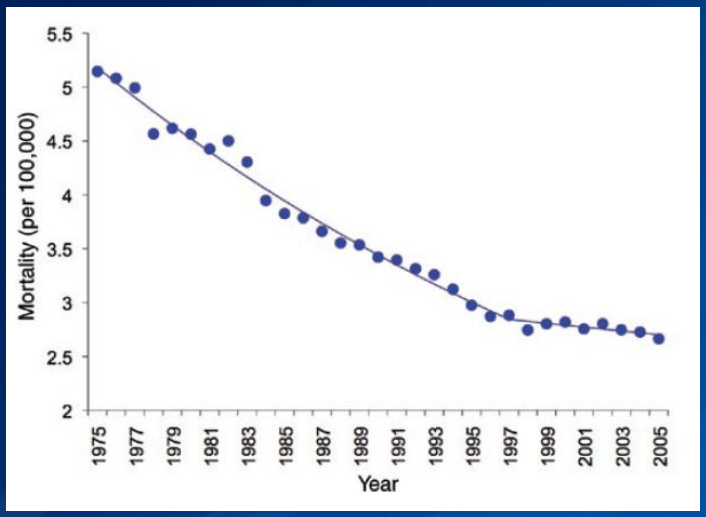
National Cancer Institute. *SEER Cancer Statistics Review, 1975-2006.* Available at: http://seer.cancer.gov.

Cancer Survival Rates in the US



National Cancer Institute. *SEER Cancer Statistics Review, 1975-2006.* Available at: http://seer.cancer.gov.

Childhood Cancer Mortality Rate



Balis FM, et al. *Clin Pharmacol Ther.* 2009;85:127-129.
National Cancer Institute. *SEER Cancer Statistics Review, 1975-2006.* Available at: http://seer.cancer.gov.

Where Is the Greatest Need?

- Cancer type
  - Hematological malignancies
  - Solid tumors
- Cancer stage
  - Local relapse
  - Metastatic disease
- Age
  - Infants
  - Adolescents and Young Adults (AYA)

Balis FM, et al. *Clin Pharmacol Ther.* 2009;85:127-9.

Pediatric Phase I Studies

- PubMed review performed
  - Published in January 2008 – April 2009
  - "Phase I Study" and "Phase I Trial"
  - "Cancer"
  - "All Children (0-18 years)"
  - English language

Pediatric Phase I Studies

- Literature review results
  - 53 citations
    - 27 citations involving pharmacological treatment modalities
      - 24 studies enrolling patients ≤ 18 years of age
- Adult comparative information (“19+ years”)
  - 282 citations returned
    - Approximately 185 citations involving pharmacological treatment modalities

Pediatric Phase I Studies

Tumor Type	Studies* (N=24)
Solid tumors (all types)	22
Central nervous system	6
Neuroblastoma	3
Melanoma	1
Retinoblastoma	1
Leukemia and/or lymphoma	2
Other (neoplastic meningitis)	1

* Numbers do not sum to 24 as some studies have overlap with respect to entry criteria and characteristics. See Appendix I for additional details of studies.

Pediatric Phase I Studies

Study Characteristic	Studies* (N=24)
Adult vs pediatric focus	5 vs. 19
Newly diagnosed vs. relapsed/refractory disease	6 vs. 19
Enrollment of infants (age ≤ 1 year)	8
Enrollment of toddlers/older children (> 1 -- < 12 yrs)	21
Enrollment of adolescent/young adults (≥ 12 years)	23
Reporting of pharmacokinetic data	14

* Numbers do not sum to 24 as some studies have overlap with respect to entry criteria and characteristics. See Appendix I for additional details of studies.

Pediatric Phase I Studies

Therapeutic Modality	Studies (N=24)
1. "Traditional" cytotoxic chemotherapeutics	11
2. Molecularly targeted therapies	5
3. Combination therapy (1 + 2)	4
4. Other therapies (vaccines, cellular therapies, etc.)	4

See Appendix I for additional details of studies.

Historical Challenges

- Cancer is a rare disease in children
- Eligibility criteria can be difficult to meet
- Obtaining informed consent and assent
- Adult subject constraints
  - Maximum tolerated dose from adult Phase I studies
  - Pharmacokinetic measurements and differences
  - Toxicity profiles
  - Long-term data

Balis FM, et al. *Clin Pharmacol Ther.* 2009;85:127-9; Berg SL. *Oncologist*. 2007;1336-43;
Kim A, et al. *Oncologist*. 2008;13:679-89; Lee DP, et al. *J Clin Oncol.* 2005;23:8431-41;
Devine S, et al. *Pediatr Clin North Am*. 2008;55:187-209; Kodish E. *J Pediatr.* 2003;142:89-90;
Abdel-Rahman SA, et al. *Clin Pharmacol Ther*. 2007;81:484-94.

Historical Challenges

- Time
  - Delay in starting trials and finishing them
- Money
  - Pharmaceutical company interest
  - Direct vs indirect costs

Balis FM, et al. *Clin Pharmacol Ther.* 2009;85:127-9; Berg SL. *Oncologist*. 2007;1336-43;
Kim A, et al. *Oncologist*. 2008;13:679-89; Lee DP, et al. *J Clin Oncol.* 2005;23:8431-41;
Devine S, et al. *Pediatr Clin North Am*. 2008;55:187-209; Kodish E. *J Pediatr.* 2003;142:89-90;
Abdel-Rahman SA, et al. *Clin Pharmacol Ther*. 2007;81:484-94.

Where Do We Go From Here?

- New trial design – the rolling six design
  - Replaces traditional 3 + 3 design
  - Allows for 2-6 patients to be enrolled concurrently at a particular dose level
    - Dose level is based on current enrollment
  - Simulated studies using discrete event simulation

Barrett JS, et al. *Clin Pharmacol Ther.* 2008;84:729-33.
Barrett JS, et al. *Comput Methods Programs Biomed.* 2008;90:240-50.
Skolnik JM, et al. *J Clin Oncol.* 2008;26:190-5.
Hartford C, et al. *J Clin Oncol.* 2008;26:170-1.

Where Do We Go From Here?

- Rolling six design advantages
  - Duration of study time is shortened
  - Decrease in study accrual suspensions
  - Decrease in eligible patients not being able to enroll on trial
  - Increase in number of participants?
  - No increase in the number or severity of toxicities?

Barrett JS, et al. *Clin Pharmacol Ther.* 2008;84:729-33.
Barrett JS, et al. *Comput Methods Programs Biomed.* 2008;90:240-50.
Skolnik JM, et al. *J Clin Oncol.* 2008;26:190-5.
Hartford C, et al. *J Clin Oncol.* 2008;26:170-1.

Where Do We Go From Here?

- Rolling six design disadvantages
  - Prospective study lacking
  - More pediatric patients may experience a dose-limiting toxicity if not previously seen in adult Phase I studies

Barrett JS, et al. *Clin Pharmacol Ther.* 2008;84:729-33.
Barrett JS, et al. *Comput Methods Programs Biomed.* 2008;90:240-50.
Skolnik JM, et al. *J Clin Oncol*. 2008;26:190-5.
Hartford C, et al. *J Clin Oncol.* 2008;26:170-1.

Where Do We Go From Here?

- Shift in therapies from cytotoxic chemo to molecularly targeted agents
  - Do pediatric malignancies have the same molecular markers and pathways?
  - What are the endpoints for study?
  - Most small molecules are “flat dosed” in adults
    - One size does not fit all in pediatrics
  - Formulation availability

Balis FM, et al. *Clin Pharmacol Ther.* 2009;85:127-9.
Abdel-Rahman SA, et al. *Clin Pharmacol Ther*. 2007;81:484-94.

Where Do We Go From Here?

- Disclosure of information
  - Increasingly, people want access to information
    - Both parents and adolescents value the offer of returning results whether positive or negative
    - Both parents and adolescents feel strongly they have a right to results of research delivered in a timely manner
    - Information is useful for future considerations and decisions about treatment and follow-up

Fernandez CV, et al. *J Clin Oncol.* 2009;27:878-83; Fernandez CV, et al. *Cancer.* 2003;97:2904-9; Partridge AH, et al. *J Clin Oncol.* 2009;27:838-9; Fernandez CV, et al. *J Pediatr Hematol Oncol.* 2003;25:704-8; Fernandez CV, et al. *Pediatr Blood Cancer.* 2007;48:441-6.

Summary

- The number of Phase I studies performed in pediatric cancer patients continues to increase
- As new molecular entities become available, the design and conduct of pediatric oncology Phase I trials will evolve
- Disclosure of information relating to pediatric oncology studies is expected to increase

This Year's Other Notable Papers

- **Long-Term Results for Children with High-Risk Neuroblastoma Treated on a Randomized Trial of Myeloablative Therapy Followed by 13-cis-Retinoic Acid: A Children's Oncology Group Study**
  - Matthay KK, et al. *J Clin Oncol*. 2009;27:1007-13.
  - Update of 1999 *New England Journal of Medicine* study with long-term outcome information showing 13-cis-retinoic acid improves survival in high risk neuroblastoma patients following consolidation therapy
- **What Determines the Outcomes for Adolescents and Young Adults with Acute Lymphoblastic Leukemia Treated on Cooperative Group Protocols? A Comparison of Children's Cancer Group and Cancer and Leukemia Group B Studies**
  - Stock W, et al. *Blood*. 2008;112:1646-54.
  - Comparisons of outcomes between patients (16-20 years) with ALL demonstrating more favorable outcomes for patients treated according to CCG studies over CALGB studies

This Year's Other Notable Papers

- **Renal Late Effects in Patients Treated for Cancer in Childhood: A Report from the Children's Oncology Group**
  - Jones DP, et al. *Pediatr Blood Cancer*. 2008;51:724-31.
  - Literature-based review of renal toxicites and corresponding therapeutic interventions in children treated for cancer
- **Hematopoietic Stem Cell Transplantation for Bone Marrow Failure Syndromes in Children**
  - Myers KC, et al. *Biol Blood Marrow Transplant*. 2009;15:279-92.
  - Review discussing the evolution of and current role of transplantation for management of children with bone marrow failure syndromes with and emphasis on aplastic anemia and Fanconi anemia

Self-Assessment Questions

1. Typically, the starting dose for agents studied in pediatric Phase I studies is what percentage of the corresponding adult maximum tolerated dose?
   a. 50%
   b. 80%
   c. 90%
   d. 110%

2. The US mortality rate for pediatric cancer patients is best described by which of the following statements?
   a. Deaths from childhood cancer continue to decrease today although the rate of decline has leveled off since the late 1990's
   b. Deaths from childhood cancer continue to decrease today and the rate of decline has increased since the late 1990's
   c. Deaths from childhood cancer have remained the same for the past three decades
   d. With increases in survival rates, cancer now represents the fourth leading cause of all deaths in children

Answers: 1.) B; 2.) A; 3.) B; 4.) C

Self-Assessment Questions

3. The need for Phase I studies in pediatric patients remains strong, particularly in patients with certain malignancies. Which of the following patients is most likely to be enrolled on a Phase I study?
   a. A 2-year old girl with newly diagnosed standard risk acute lymphoblastic leukemia
   b. A 3-year old boy with neuroblastoma who has recurrent disease three months following the combination of high-dose chemotherapy with autologous stem cell rescue and isotretinoin
   c. A 7-year old girl with newly diagnosed juvenile pilocytic astrocytoma and undergoes gross total resection of tumor
   d. A 14-year old boy with newly diagnosed osteosarcoma of the left distal femur with evidence of a single pulmonary lesion

4. When compared to the traditional 3 + 3 design, the rolling six design for pediatric Phase I studies has all of the following potential advantages EXCEPT:
   a. Shorter time to completion
   b. Fewer study accrual suspensions
   c. Fewer eligibility criteria necessary for study enrollment
   d. Increase in the number of study participants

Answers: 1.) B; 2.) A; 3.) B; 4.) C