National Collaborative Study Groups in Oncology: Structure, Benefits and Challenges

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A Brief History of Leukemia Therapy

1940’s- all leukemias uniformly fatal.

Limited tools to characterize or understand the leukemias

No therapeutic options available to slow or prevent the rapid, inevitable death of the patient.
A Brief History of Leukemia Therapy

Sidney Farber—The father of modern chemotherapy

Assistant Professor of Pediatrics and Pathology at the Children’s Hospital Medical Center and Harvard Medical School

The role of Folic Acid and its antagonists in cancer cell growth

Development of amniopterin and actinomycin D, et al.
A Brief History of Leukemia Therapy

MONOTHERAPY

1947 Monotherapy first initiated with the introduction of folic acid antagonists, aminopterin, etc. 10/16 children responded. First remissions observed

1940’s First cooperative trial using nitrogen mustards (Univ. of Utah, Tufts, Univ of Oregon, US Army).

1950’s Frequent remissions observed, but transient

1960’s Remissions were commonly achieved, but lasted less than one year. DFS < 1 % “Let Them Die in Peace”

Miller DR. British Journal of Hematology 134:20-26, 2006
A Brief History of Leukemia Therapy

MONOTHERAPY

Significant Findings

1) There was a background of normal hematopoietic cells which could recover if the leukemia was suppressed.

2) There was heterogeneity in the response, hence the recognition of genetic variability.

3) Hope. Additional research may yield therapy with more prolonged responses

SURVIVAL WAS DISMAL !!!
National Collaborative Study Groups in Oncology: Structure, Benefits and Challenges

1950-60’s Development of new drugs and new drug classes with synergistic or additive effects were introduced and combined (1958*)

1950-60’s Improvement in transfusion techniques and components usage

1950-60’s Development of effective antibiotic therapy for infectious complications.

1950-60’s Establishment of federally funded cooperative cancer chemotherapy groups.

National Collaborative Study Groups:

Pediatric Cancer Trial Groups: a model for success:

• History, Lessons Learned, Benefits Gained
Pediatric Oncology Group - POG

1955 The NCI Clinical Studies Panel proposed the creation of “Collaborative Groups” to advance the study and cure for leukemia.

1956 SWCCSG was formed as a pediatric oncology group and in ...

1958 ...grew to include adult malignancies. The purpose of the group was to evaluate new chemotherapy agents.
Pediatric Oncology Group-POG

1971 SWCCSG was divided into two distinct groups, pediatric and adult, with their own organization and in 1973 changed it’s name to SWOG (SouthWest Oncology Group).

1979 The pediatric portion became independent and formed POG (Pediatric Oncology Group), Consisting of 1103 oncologists from 75 institutions.
1955 The NCI Clinical Studies Panel proposed the creation of “Collaborative Groups” to advance the study and cure for leukemia.

Under the auspices of the NCI, The Acute Leukemia Cooperative Chemotherapy Study Group A was formed from a group of pediatric oncologists from nine institutions. It came to be known as “Leukemia Group A” studying only acute leukemia and only chemotherapy.
Children’s Cancer Group-CCG

1958 The group created geographic subgroups which developed standard criteria for evaluating disease status response to therapy.

1965 The group expanded studies to include Wilms’ tumor and ANLL. The group’s name was changed to the Children’s Cancer Study Group-CCSG.
1968 The group recognized the need for a multidisciplinary team approach and created discipline committees including pathology, pediatric surgery and radiation therapy. Additional disciplines have been added since.

1972 Study information became computerized and a Group Operations Office was formed which included Data and Statistics Centers as well as the Group Chair’s office.
National Collaborative Study Groups

2000 Under direction of the National Cancer Institute the four cooperative groups for children’s cancer were merged into one group named COG (Children’s Oncology Group).

2001 The first group-wide competitive grant from COG was submitted to the NCI for funding.
COG: Children’s Oncology Group: Structure

COG is an international research organization founded and supported by the NCI. It was formed in 2000 from four cooperative groups: POG, CCG, NWTSG and IRSG - each with their own unique history.

COG members include over 5,000 pediatric oncologists from 240 medical centers in the US, Canada and Australia.
**COG-STRUCTURE**

**Membership:**

**Institutional Membership Criteria**

- Must meet criteria for a pediatric cancer center as outlined
- Must be an independent hospital, medical center or research institute where individual members meet qualifications
- Must treat a minimum of 12 newly diagnosed cancer patients each year based on a rolling average
COG-STRUCTURE

Membership:

Individual Memberships - each site has:

- Principal Investigator
- Full Individual Members
- Associate Members

*Individual and Institutional membership are subject to probation and/or suspension if there is a failure to meet membership commitments*
COG-STRUCTURE

Committees:
Committees are created to oversee the organization of the group and its research efforts:

- **Standing Committees**: Executive, Voting Body, Nominating, Performance Monitoring, Membership and Data Monitoring
- **Discipline Committees**
- **Scientific Committees**
- **Other Ad Hoc Committees and Task Forces**
COG-STRUCTURE

Executive Committee

- Composed of 15 members from different committees and the Group Chair
- Responsible for strategic planning, policies and procedures, membership issues, resource allocation, financial decisions, etc
Voting Body

- Composed of Principal Investigators from each institution
- Responsible for ratification of amendments from Executive Committee, election of the Group Chair, approval of membership issues and appeals
COG-STRUCTURE

Group Operations Office

- Directed by the Group Chair
- Responsible for administration, managing meetings, membership processing, protocol support, and preparing and managing grants
COG-STRUCTURE

Group Statistics Department

- Directed by the Group Statistician
- Responsible for statistical collaboration on study design, protocol development, study conduct, data analysis, research data system operations, group data management, data archiving, and regular reports submissions to the Group Chair and data monitoring committee
Mission Statement:
To cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care

www.childrensoncologygroup.org/
COG: Lessons Learned

- Competition decreases ability to answer important questions
  - Difficult to ask very specific questions in common diseases
  - Impossible to study rare diseases adequately
- Willingness to collaborate in large groups is crucial to success
  - Give up individual identity
  - Good ideas can be refined into outstanding ideas by group discussions
COG: Lessons Learned

- Cross-disciplinary interactions permit novel ideas to be introduced
  - Wilms Tumor Study Group: 4 yr survival increased from 20% to 96% with post-nephrectomy chemotherapy
  - Preoperative chemotherapy for sarcomas dramatically increased survival
- Prioritization can be challenging
  - Tendency to ask research questions based on financial considerations rather than by real needs
COG: Lessons Learned

- Young Investigators
  - Tendency for “old guard” to dominate and may be a challenge for effective integration of “new blood”
  - To address this, COG established
    - Young Investigator Committee
    - Mentorship Program that pairs a new member with an established investigator
COG: Challenges

- Cooperative Group Funding
  - Reimbursement to a site is $2,000/patient for a therapeutic study and $500/patient for a biology study.
  - Cost of doing a therapeutic COG study is $9,000 to $20,000/patient. Cost for a Biology study is $350- $1000/patient.

- Reward for “number” of patients enrolled.
  - Rarer tumors do not get adequate study.
Summary

For rare diseases, national collaborative study groups

- Have demonstrated success in COG by improving survival and quality of life
- Demonstrate that the group is smarter than any individual – power of collective intelligence
- Have provided a foundation for future investigations: data sets and tissue repository
- Permit clear delineation of future directions and future goals
- Provide a venue for advocacy and public awareness
COG: Children’s Oncology Group

COG currently conducts over 150 concurrent studies of childhood cancer including basic science, translational research and clinical trials. There are currently over 40,000 children with cancer being managed by these protocols.

COG research has been responsible for almost all of the important improvements in childhood cancer. Since the inception of cooperative groups until now, cure rates for childhood cancer have improved from <10% to greater than 80%.
Background: Kaplan-Meier Analyses of Event-free Survival (Panel A) and Overall Survival (Panel B) in 2628 Children with Newly Diagnosed ALL
### Approximate ALL Cure Rates

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<thead>
<tr>
<th>Decade</th>
<th>Pediatrics</th>
<th>Adults</th>
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<tbody>
<tr>
<td>1960’s</td>
<td>30-40%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>1970’s</td>
<td>40-50%</td>
<td>10%</td>
</tr>
<tr>
<td>1980’s</td>
<td>50-70%</td>
<td>20-30%</td>
</tr>
<tr>
<td>1990’s</td>
<td>65-80%</td>
<td>30-40%</td>
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1) Why are the cure rates different?
2) What about adolescent and young adults (AYA)?
1) Why are the cure rates different?

Often cited explanations:

- Different disease genetics.
- Children can endure more aggressive treatment protocols than adults can tolerate.
- Parents increase compliance with oral medications.
- A better supportive care network and superior resources available for pediatric patients.
- 90% of pediatric hematologists are in academic practice vs <10% of adult hematologists, so better access to new therapeutic protocols.
- Pediatricians are better doctors (that is what the pediatricians say).
1) Why are the cure rates different?

Often cited explanations:

- Different disease genetics. (Definitely YES!!!)
- Children can endure more aggressive treatment protocols than adults can tolerate. (Probably yes)
- Parents increase compliance with oral medications. (?!?!)
- A better supportive care network and superior resources available for pediatric patients. (unlikely to make large impact)
- 90% of pediatric hematologists are in academic practice vs. <10% of adult hematologists, so better access to new therapeutic study protocols. (probably some impact)
- Pediatricians are better doctors (that is what the pediatricians say). (Of course this is true)
2) What about adolescent and young adults (AYA)?

Comparison between AYA treated on Pediatric (CCG) or Adult (CALGB) Protocols

- Age 16-21
- CCG treated 1989-1995 (N = 196 patients)
- CALGB treated 1988-1998 (N = 103 patients)
- Matched for WBC > 50k, T cell immunophenotyping and t(9;22).

<table>
<thead>
<tr>
<th>Protocol</th>
<th>CR rate</th>
<th>ES</th>
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<tbody>
<tr>
<td>CCG</td>
<td>96%</td>
<td>64%</td>
</tr>
<tr>
<td>CALGB</td>
<td>93%</td>
<td>38%</td>
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</tbody>
</table>
2) What about adolescent and young adults (AYA)?

- 15-21 year olds may be treated by either a pediatric or adult hematologist depending on referring physician.
- Many Children’s Hospitals have upper age limits.
- In the USA > 85% of patients age 1-14 with cancer are treated on an NCI sponsored clinical trial. Age 15-29 < 36% on a clinical trial.
- AYA have disease that is clinically and biologically distinct from children and adults.
- AYA patients with B cell had higher incidence of CALLA neg, higher Hb, less lymphomatous features.
- AYA patients with T cell had higher Hb, hepatosplenomegaly.
- The t(9;22) increase in incidence with increasing age.
- Lower incidence of t(12;21) in AYA compared to younger age.
- AYA with increased in vitro drug resistance to PDN and DNR.

Nachman J. Br J of Hem. 130:166-73, 2005
Primary ALL cells → In vitro sensitivity and microarray analysis → Gene-expression profile → Treatment outcome

To identify genes that are associated with drug resistance and treatment outcome.
Implications/Future Directions

- Individualized ALL therapy
- Algorithms for risk strata to include pharmacogenetic data
- Monitoring ALL tx pts periodically for pharmacogenetic changes (ie DHFR upreg)
Implications/Future Directions

1950-1960
Individual
Patient
Treated

1970-2010
Cooperative
Group
results
dictate
therapy

>2010
Heritable
factors &
tumor specific
factors
dictate therapy
in cooperative
group context.