commentary

National collaborative study groups: Structure, benefits gained and potential for rare genetic diseases

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Multidisciplinary participation in national collaborative study groups has resulted in significant improvements in patient outcomes and provided substantial contributions to our scientific understanding of a variety of diseases. Arguably the most successful of the cooperative groups have been the pediatric cancer trial groups, which in over 35 years of existence have contributed to survival rates that have improved from <10% to >70%.[1] From their earliest beginnings pediatric cancer trial groups have maintained a linkage between the laboratory and clinical trials with discoveries in each fueling new investigations in the other.[2] A review of the history of these cooperative groups, lessons learned and benefits gained can provide a model for the potential development of a rare genetic disease national collaborative group.

HISTORY OF PEDIATRIC CANCER TRIAL GROUPS

Children's Oncology Group (COG)

The COG is an international research organization founded and supported by the National Cancer Institute (NCI). It was formed in 2000 from four cooperative groups: the Pediatric Oncology Group (POG), the Children's Cancer Group (CCG), the National Wilms' Tumor Study Group (NWTSG) and the Intergroup Rhabdomyosarcoma Study Group (IRSG) each with their own unique history.[3] The first group-wide competitive grant from COG was submitted to the NCI for funding. Membership now includes over 5,000 pediatric oncologists from 240 medical centers in the US, Canada and Australia. COG supports over 150 concurrent studies of childhood cancer including basic science investigations, translational research and clinical trials. There are currently over 40,000 children with cancer being managed under these protocols. Research by COG and its predecessors has been responsible for almost all of the important improvements in childhood cancer. These improvements have been iterative as well as quantal, and all have been objectively evaluated, thus providing an evidence-base for changes in clinical practice.

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Pediatric Oncology Group (POG)

In 1955, the NCI Clinical Studies Panel proposed the creation of "Collaborative Groups" to advance the study of and cure for leukemia. In 1956 the Southwest Cancer Chemotherapy Study Group (SWCCSG) was formed as a pediatric oncology study group and in 1958 grew to include adult malignancies. The purpose of the group was to evaluate new chemotherapy agents. In 1971 the SWCCSG was divided into two organizationally distinct groups, pediatric and adult, and in 1973 changed its' name to SWOG (Southwest Oncology Group). In 1979 the pediatric portion became independent and formed POG (Pediatric Oncology Group), consisting of 1,103 oncologists from 75 institutions.[3]

Children's Cancer Group (CCG)

To meet the 1955 Clinical Studies Panel mandate for "Collaborative Groups" the NCI formed The Acute Leukemia Cooperative Chemotherapy Study Group A 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. In 1958 the group created geographic subgroups that developed standard criteria for evaluating disease status and response to therapy. In 1965 the group expanded studies to include Wilms' tumor and acute nonlymphoblastic leukemia (ANLL). The group's name was changed to the Children's Cancer Study Group (CCSG).

In 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. In 1972 study information became computerized and a Group Operations Office was formed that included Data and Statistics Centers as well as the Group Chair's office. In 1982 the group expanded the discipline committees to include nursing, radiology and psychology. Scientific committees were formed to oversee new agents, cancer biology, epidemiology, late effects of therapy and others. Centralized reference laboratories and tissue banking were established. In 1990, a tax exempt charitable foundation was established to help attract private sector support for the consortium's work.[3]

Solid tumor study groups

In 1964 the National Wilms Tumor Study Group (NWTSG) was formed. Multi-disciplinary participation resulted in a striking improvement in the four-year survival rate for chil-

dren with Wilms tumor from 20% to 96% in the most favorable stages.[4]

In 1966 the Intergroup Rhabdomyosarcoma Study Group (IRSG) was formed and survival tripled in children from 25% to 75%.[3]

STRUCTURE OF COG

Membership

There are both individual and institutional memberships available within COG. Individual memberships are available to pediatric oncologists and specialists in related disciplines engaged with COG in North America, Europe and Australia. Institutional Membership Criteria were created to be as inclusive as possible, yet maintain a level of competency. An institution must meet criteria for a pediatric cancer center as outlined by the American Academy of Pediatrics Section on Hematology/Oncology.[5] It must be an independent hospital, medical center or research institute where individual members meet the established qualifications (see below). It must treat a minimum of 12 newly diagnosed cancer patients each year based on a rolling average. It must have a commitment to enroll patients in both therapeutic and nontherapeutic trials with a minimum of 6 patients and 2 patients, respectively. It must maintain compliance with all of the documentation requirements as outlined by COG.

Individual memberships include the following categories: a site Principal Investigator (site PI), Full Individual Members, and Associate Members. The site PI is responsible for the research integrity at his or her institution, prioritization of protocol submissions for the institution's regulatory approval, and he or she recommends individuals from the site for membership. The site PI's also represent their institutions as members of the Voting Body of COG, giving approval for new protocols, new institutional memberships, constitutional amendments and election of leaders among other responsibilities (see Voting Body below). The PI's must be Board certified in their specialties. Regular attendance and participation at meetings is required. A Full Individual Member and Associate Member must be from a COG member institution or from one of the COG Operations Offices and must meet appropriate discipline criteria. A Courtesy Membership is reserved for an individual who wishes to participate actively in COG but whose institution is not a member. This level of membership allows registration of patients, but enrollment must occur at a COG member institution. The individual Courtesy Member may participate in committees, but may not chair them. Individual and institutional memberships are subject to probation and/or suspension if there is a failure to meet membership commitments.

Committees and support offices

A committee structure was created to oversee the organization of the group and its research efforts. This structure includes Standing Committees (Executive, Voting Body, Nominating, Performance Monitoring, Membership, Data Monitoring), Discipline Committees, Scientific Committees and other Ad Hoc Committees and Task Forces. The Executive Committee is composed of 15 members from different committees and the Group Chair. It is responsible for strategic planning, policies and procedures, membership issues, resource allocation, financial decisions, etc. The Voting Body is composed of Principal Investigators from each institution, and is responsible for ratification of amendments from the Executive Committee, election of the Group Chair, and approval of membership issues and appeals. The Scientific and Discipline Committees take leadership roles in developing priorities and goals for protocol development and implementation in various disease categories, contributing their expertise to the process.

Support offices and core resources have been developed for the purpose of both administrative support and centralized review. The Group Operations Office is directed by the Group Chair, and is responsible for administration, managing meetings, membership processing, protocol support, and preparing and managing grants. The Group Statistics Department is directed by the Group Statistician. This department is responsible for statistical collaboration on study design, protocol development, study conduct, data analysis, research data system operations, group data management, data archiving, and regular report submissions to the Group Chair and Data Monitoring Committee. Centralized Reference Laboratories and Review Centers (for review of diagnostic pathology, cytogenetics, etc.) help provide quality assurance, study eligibility confirmation and uniform review.

PEDIATRIC CANCER TRIAL GROUPS: LESSONS LEARNED

There are many lessons that can be learned from over 35 years of experience with the pediatric cancer cooperative groups. Perhaps the primary lesson is that a willingness to collaborate in large groups is crucial to success. Competition among individual investigators and institutions decreases ability to answer important questions, especially in uncommon diseases, and therefore it is impossible to study rare diseases adequately without cooperation. Collaboration often means giving up individual identity for the greater good of scientific advancement and improved patient care. Cross-disciplinary interactions permitted novel ideas to be introduced. Experience has shown that good ideas can be refined into outstanding ideas by group discussions.

Collaboration between different disciplines may lead to dramatic improvement in survival and there are several examples of this. Wilms' tumor was initially treated with surgery alone and patients had a dismal four-year survival of only 20%. Cross-disciplinary interactions lead to the addition of postnephrectomy chemotherapy and survival eventually reached as high as 96% for favorable stages. Similarly, surgical resection of sarcomas typically carried a fairly high rate of relapse, but when preoperative chemotherapy was introduced survival dramatically increased.

The "decentralized" system used in cooperative groups have allowed patients with even the rarest of diseases to be managed locally with state-of-the-art therapy while adding to the educational opportunities for local investigators and their trainees. In addition, many cooperative groups have developed "satellite" sites that have a relationship with larger institutions. This has allowed these smaller and often more remote sites access to resources not otherwise available for their patients. In turn, this has resulted in a larger capture of patients with rare diseases.

Tissue and DNA repositories have been created and samples added over the years, providing an invaluable resource with which current and future technologies can mine even the rarest of diseases. These repositories have already facilitated gains in basic science and translational research. Longitudinal, biobehavioral, psychosocial and quality of life studies have been possible with the large database and sophisticated statistical methodologies. The use of centralized reference labs set standards for local laboratories to achieve when particular tests later become decentralized. Participating sites are regularly audited to assure high quality data for analysis. Radiology and nuclear medicine studies are often reviewed centrally as well as at the local institution to corroborate findings. The greatest accomplishment of all is clearly the legacy of patients cured of diseases previously considered incurable.

Significant problems remain, however, not the least of which is a shortfall of funding necessary to finance these diverse efforts.[1] In addition, only 5–20% of 15 to 25-year-olds are entered in cooperative group studies as compared to 65% of those <15 years of age.[6] The five-year outcomes for those 15–25 years of age not treated on a cooperative group trial protocol are inferior.[7] In addition, not all children with cancer are being registered through the cooperative groups, with reliance on state cancer registries to fully capture a more accurate number,[8] suggesting the need of a national registry to supplement and verify cooperative group registrations.

POTENTIAL FOR RARE GENETIC DISEASES

It is clear that cooperative groups for childhood cancer have led to significant advances in the understanding and treatment of pediatric malignancies despite the fact that they are relatively rare. The creation of a national or international cooperative group for rare genetic diseases could hold similar if not greater potential benefit. The possibilities appear endless for attaining iterative as well as quantal improvements in outcome.

Collaborations across disciplines such as clinical geneticists, biochemical geneticists, hematologists, neurologists and others can enrich ideas and make significant contributions, such as have already been demonstrated in Gaucher disease. In addition, pooling of patients with rare disorders greatly improves the statistical power of the investigations. The establishment of tissue and data repositories would facilitate current and future studies involving data mining for new ideas, epidemiological studies of potential gene-environment interactions and ethnicity relationships, although this would only be as good as the quality of the data in the bank. A collaborative group in genetic diseases also would provide a forum for intensely focused discussion on a rare disease.

The establishment of an international collaborative group for rare genetic diseases could serve to raise public awareness. This improved public awareness in turn could lead to the establishment of a Foundation associated with the collaborative research group that could effectively carry out fund raising, advocacy, legislative lobbying, increased public awareness, and provide grants for young investigators. In addition, the establishment of this collaborative group could help facilitate closer communication between the NIH and the research group leading to a clear delineation of goals, and identification and prioritization of fundable projects.

Another lesson learned by COG and to which the genetics community should be attentive involves young investigators. There had been a tendency in COG for the "old guard" to dominate, and this was recognized to be a challenge for effective integration of "new blood." To address this issue, COG established the Young Investigator Committee and a Mentorship Program that paired a new member with an established investigator. These features should be considered in establishing a genetics cooperative group.

It is also important to keep in mind potential differences between rare genetic disease and childhood cancer when applying the principles learned from national collaborative groups. The large number and diversity of specialists in genetic diseases may make the formation of a collaborative group much more challenging, than it was for the smaller group of cancer providers. Philanthropic support is often more disease exclusive, making it difficult to develop a broad community base of advocacy and fundraising for a large collaborative group. These and other potential obstacles must be considered during the development of such a group for medical genetics in order to optimize its effectiveness.

SUMMARY

For rare diseases, national and international collaborative study groups have a proven record of success by improving survival and quality of life, demonstrating that the group is smarter than any individual, providing a foundation for future investigations including data sets and tissue repository, permitting clear delineation of future directions and future goals, and providing a venue for advocacy and public awareness. The time has come for medical genetics to explore the possibility of establishing a national or international collaborative study group. The American College of Medical Genetics (ACMG) is taking the lead in planning such an activity and should proceed despite the challenges facing the NIH at this time. Such a cooperative study effort will be required to make effective progress to improve outcomes for patients with genetic disease.

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