

Clinical Advances in Pediatric Hematology & Oncology: Cooperative Group Research

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The dramatic advances in treatment for most childhood cancers over the past 40 years are the result of a concerted, systematic effort to improve treatment outcomes through collaborative, multi-center clinical trials. Fifty years ago, most cancers were virtually fatal for children, with survival rates lower than 10%. In 1956, the National Institutes of Health sponsored the development of a consortium of academic institutions to pool their patient populations and conduct investigations of new drugs and combinations in acute leukemia, the most common form of childhood cancer. This was the nation's first cooperative clinical trials group and emerged as the legacy Children's Cancer Group. Pediatric divisions of other groups coalesced, forming the Pediatric Oncology Group. Early successes resulted in disease-focused groups, the National Wilms Tumor Study Group, and the Intergroup Rhabdomyosarcoma Study Group.

In an unprecedented move for greater efficiency and collaboration, these 4 legacy pediatric cooperative groups merged in 2000, forming the Children's Oncology Group (COG) with the intention of consolidating their efforts to accelerate the goal of improving outcomes, identifying cause(s), and ultimately preventing cancer in infants, children, and adolescents. The formation of the COG marked the beginning of a new era in the continuing fight to cure and prevent all types of childhood cancer. The COG brings together the best research institutions and leaders in the field of childhood cancer treatment and research.

The COG is composed of over 5,000 physicians, nurses, epidemiologists, and others who provide care for children with cancer, as well as laboratory scientists who perform translational research. Members are located at more than 230 of the top medical institutions across the United States, Canada, Australia, and New Zealand, in

addition to several members in Western Europe. These institutions include children's hospitals, university medical centers, cancer centers, and community hospitals with approved pediatric cancer programs. Simply stated, the mission of COG is to cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care.

To carry out its mission, COG:

- designs and conducts clinical trials to define the best treatments;
- conducts laboratory research that translates into improved therapy;
- identifies the causes of childhood cancer; and
- conducts research to improve quality of life and long-term survival.

Since the merger, concerns about the lack of competition with a single pediatric cooperative group, the potential impact on intellectual creativity, and jeopardizing external, scientific peer review have surfaced. The unfortunate reality is that due to both the improved outcomes for many pediatric cancers and the current efforts at subclassification of patients both clinically and biologically to identify risk groups, the ability to do competing, randomized studies—given the population of patients in North America—is increasingly impossible. Given the number of intergroup trials required between the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG), it is for this very reason that the initial discussions and decisions regarding unification were entertained. There has been no restriction of scientific creativity; the COG continues to support single- and limited-institution pilot investigations of novel approaches to therapy. Several

recently opened studies attest to this fact. International pediatric oncologists, in particular those in Europe, provide rigorous peer review.

Using acute lymphoblastic leukemia (ALL) as an example, the power of increased numbers of patients and the evaluation of independent clinical and biologic prognostic factors that remain significant, despite profound differences in therapeutic approaches between both CCG and POG, have contributed significantly to a new paradigm in risk group classification and risk-adjusted therapy approaches that could only be planned and implemented because of the merger. This example extends to other cancers, including neuroblastoma, brain tumors, and sarcomas. In addition, there is intense, healthy, and productive scientific competition in many disease areas in pediatric cancer between COG and its international colleagues and cooperative group counterparts. This healthy competition is a direct result of increasing amalgamation of clinical research efforts in the European nations as well.

As a result of the merger, a single central coordinating site and operations center was established that assumed responsibility for the entire new group as well as for the coordination and management of more than 70 open legacy group clinical trials. It should be noted that this single location in Arcadia, Calif., operates with no increase in the number of staff positions than it had when it served as the group operations center for a single cooperative group, the CCG.

The initial decision to base the COG Research Data Center at the former POG Statistical Center at the University of Florida in Gainesville was precipitated by the departure of several key staff and senior statistician leaders. An electronic remote data entry system (RDES) failed operationally and, although envisioned as being able to rapidly accommodate an expanding number of studies under development, it was unable to respond and ultimately failed. This required extensive maintenance to support those legacy studies managed on the original RDES. Reorganization of the Statistics and Data Center was necessary. An enhanced RDES (eRDES) was designed and developed over a period of 18 months with approval from the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) at a cost of nearly \$1 million, none of which was provided by the NCI. Intensive use of programmers, database administrators, and statistical staff to the development of the eRDES prevented the timely opening of new trials. Nonetheless, it was obvious that an enhanced operational system was required to obtain the optimal efficiency that was planned in opening newly designed studies; such studies would depend heavily on novel study builder software that would significantly reduce expensive and time consuming programmer resources. In November 2004, the new

eRDES came online; since that time, over 54 new studies have opened. To provide perspective, the original RDES accommodated the opening of 60 studies over a period of 6.5 years. We project an ability to open 1–2 studies per week. Currently, there is no backlog of approved studies awaiting RDE development.

A direct result of the new eRDES has been the significant increase in patient enrollment on COG trials (approximately 40%). Over 8,600 patients have enrolled on COG trials this year, an increase of 2,600 patients when compared to last year. Over 11,000 newly diagnosed patients were registered at COG institutions. Almost 90% of those patients were enrolled on a COG study.

Another significant achievement has been the completion of a group-wide survey of principal investigators and Institutional Review Board (IRB) chairs demonstrating the need for centralization of independent scientific and ethical review of COG studies to facilitate review and approval at over 230 study sites. In addition to the enormous human and financial cost of such a review at each individual study site, quality and consistency of scientific review emerged as the major concern among both investigators and IRB chairs, dictating the need for a centralized process. COG leadership was able to present the case to the NCI and funding was made available for the development of a separate pediatric panel as a Pediatric Central IRB (PedCIRB). The NCI appointed board members for the newly constituted PedCIRB, an expansion of the NCI Central IRB (CIRB) Initiative for the central review of NCI-sponsored Cooperative Group protocols and has created standard operating procedures and policies; it has also worked closely with COG leadership to assure its success in making facilitated review possible at as many COG institutions as possible. Moreover, the PedCIRB is fully operational and began reviewing CTEP-approved COG phase II and phase III trials during their first meeting on November 22, 2004. The PedCIRB initiative was designed to provide a high level of scientific and ethical review for the protection of human research participants while reducing the administrative burden on local IRBs and clinical investigators.

The 17-person PedCIRB includes 10 physicians, 2 nurses, 1 bioethicist, 2 patient advocates, 1 pharmacist, and 1 statistician. The bioethicist and one of the advocates are also physicians. The selected PedCIRB members provide broad clinical, scientific, and ethical expertise for the review of COG treatment protocols. Additionally, the board members have a great deal of experience in the review of pediatric clinical trials, especially the special considerations that must be made for the evaluation of research involving children. The vast majority of PedCIRB members currently serve or have recently served on local IRBs, and the 2 members without local IRB experience

have Data and Safety Monitoring Board and other relevant advisory committee experience.

Since the merger, exciting new research initiatives have been developed that otherwise may never have come to fruition if separate legacy group infrastructures still existed. For example, a new classification study for ALL is in place, with reference laboratories established on both the east and west coasts of the United States to accommodate geographical distribution of diagnostic and post-therapy specimens from all of our treatment sites, which will permit the evaluation of new risk groups and risk-adjusted therapy determination. Evaluation of response by detection of minimal residual disease with therapeutic interventions in those patients who have more than .01% residual leukemia cells in postinduction marrow will be part of this 5-year approach and will be the only study worldwide to prospectively assess the prognostic value of minimal residual disease. New clinical trials in high-risk ALL, very high-risk ALL, and infant leukemia are open. A new standard-risk trial has been developed and will be ready to open as soon as current standard-risk trials are completed. Correlative biology investigations include continued investigations of gene expression profiles in leukemic cells and delineation of specific genes whose expression appears to predict a high likelihood of continuous complete remission and those in which there is low expression, associated with induction failure. Prospective evaluation of these molecular genetic prognostic factors in clinical trials are envisioned, and these studies are expected to result in the delineation of potential molecular targets that may be exploited therapeutically.

A group-wide pilot study of chemotherapy plus a targeted agent developed in the COG in newly diagnosed patients with acute myeloid leukemia is currently open. The new agent, gemtuzumab ozogamicin (Mylotarg, Wyeth), is being evaluated in an upfront setting to evaluate feasibility in combination with intensive induction chemotherapy prior to a planned randomized trial.

COG is actively investigating other new agents and currently has 17 open phase I studies of new agents. Opening of new agent studies was never affected by the delay in the development of the new RDES, as these studies were

being conducted using old paper data capture systems to keep pace with the availability of emerging new agents and the need to evaluate such in the pediatric population. The first 4 COG studies opened in the new RDES were phase I studies of new agents.

The COG has recently embarked on 2 major international collaborations in bone tumors, both Ewing sarcoma and osteosarcoma with European investigators in Germany, the United Kingdom, Austria, Scandinavia, and Italy.

For the first time in 25 years, retinoblastoma is being evaluated in pediatric cooperative group studies. Three such clinical trials in retinoblastoma are now open. The studies are aimed at preserving vision in infants and young children who were previously managed with enucleation resulting in blindness and/or radiation therapy associated with a high risk of second cancers. These clinical trials provide further fertile opportunities for correlative biology and molecular epidemiology research as well as international collaboration; plans for collaboration are being extended to Europe, South America, and India.

COG has effectively dealt with unanticipated catastrophes in the face of a flat and diminishing federal funding base. We remain honorably and passionately committed to our mission to cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care. Past success provides evidence that collaborative efforts of laboratory-based scientists and clinical investigators from multiple disciplines, conducting cooperative, multi-center clinical trials, is vital to the continued success and improvement in outcome for all children with cancer and particularly in children with those specific cancers most resistant to conventional treatment approaches. To that end, COG remains poised to exploit molecular genetic abnormalities in pediatric cancers for new targeted therapy application in combination with currently successful, conventional approaches to improve outcome results and decrease risk of toxicity. It will continue to provide evidence-based standards of care through collaborative research and assist in extending the paradigm to other childhood diseases.