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Clinical trial design in neonatal pharmacology: Effect of center differences with lessons from the pediatric oncology cooperative research experience

Cassandra Moran, DO[1], **P. Brian Smith, MD, MHS**[1,2], **Michael Cohen-Wolkowiez, MD**[1], and **Daniel K. Benjamin Jr., MD, MPH, PhD**[1,2]

[1] Department of Pediatrics, Duke University, Durham, NC

[2] Duke Clinical Research Institute, Duke University, Durham, NC

Introduction

Survival for premature neonates has dramatically improved over the past 20 years; however, there has been minimal improvement in prematurity-associated morbidities. Morbidity rates and assessment of outcomes vary across neonatology intensive care units (NICUs). Here, we address the reasons underlying these differences, note the impact that this center-variation has on trial design and interpretation, and highlight the success of the pediatric oncology efforts to develop standards of care through the conduct of multicenter clinical trials.

Pediatric Oncology Studies

Collaborative research is commonplace in pediatric oncology. By developing networks of researchers and research centers, pediatric oncologists are able to conduct large multicenter clinical trials, complete subject enrollment in a timely manner, publish the results, create new standards of care, and validate or refute existing practices. This approach has dramatically improved childhood cancer survival over the last half-century.(1) Examples of this success are the improvements in survival for patients with acute lymphocytic leukemia from <10% to an overall cure rate of 85%(1) and Wilms' tumor from <10% to >95%(stage I, favorable histology).

These and other neoplasms are now curable because of rigorous multicenter clinical trials that allowed investigators to evaluate new agents, novel therapeutic combinations, treatment duration, biological risk factors, and therapy intensification. The trials are carried out by cooperative groups of investigators. These groups lead efforts to test preclinical findings in large clinical studies, provide infrastructure to coordinate multicenter studies, monitor results of ongoing studies to ensure safety, develop tissue banks for biological and genomic studies, develop patient registries, provide statistical expertise for data analysis, develop classification systems, and ultimately establish standards of care. Most current standards of practice in oncology are the result of cooperative group clinical trials.

Four primary cooperative groups have driven pediatric oncology trials: the Children's Cancer Group, the Pediatric Oncology Group, the Intergroup Rhabdomyosarcoma Study Group, and the National Wilms' Tumor Study Group. These groups merged in 2000 to form the Children's

Corresponding Author: Danny Benjamin, MD, PhD, MPH, Associate Professor, Duke University, Pediatrics, 2400 Pratt St., Duke Clinical Research Institute, Durham, NC 27715; p: 919-668-8295; f: 919-681-9457; danny.benjamin@duke.edu.

Oncology Group (COG) which includes 230 pediatric centers that have collectively enrolled over 30,000 children in clinical trials and published >1000 manuscripts.(1) Within COG, there are multidisciplinary study committees for different types of cancer (e.g. sarcoma, neuroblastoma, and leukemia study groups) comprised of experts from oncology, pathology, radiology, radiation oncology, surgery, pharmacology, and statistics. These researchers design, implement, and interpret clinical trials to determine the best clinical management.

All participating institutions in COG undergo an official approval process prior to admission to full membership; the criteria for approval include patient volume and expertise in pediatric hematology-oncology, pediatric surgery, radiation-oncology, and other pediatric sub-specialties. Furthermore, most COG-sponsored protocols include supportive care guidelines (e.g., infection prophylaxis and treatment, management of common toxicities) and drug dosing recommendations that contribute to consistency across institutions. Additionally, centers must maintain a minimum number of open studies and adequate subject enrollment.

Neonatology Studies

Collaborative networks have also been formed in neonatology to conduct multicenter clinical trials, develop large databases to evaluate interventions, and monitor outcomes for hospitalized neonates. These networks include the Vermont/Oxford Network and the National Institute of Child Health and Human Development Neonatal Research Network (NRN). The Vermont/Oxford Network, founded in 1988, is a global network comprised of >800 institutions. It creates and maintains a database that serves as a basis for study design and provides the neonatology community insight into practice and outcome variations among tertiary care centers. The Vermont/Oxford Network does not sponsor therapeutic randomized trials but has led studies of quality improvement initiatives. The NRN, established in 1986, is comprised of 16 centers and conducts both observational studies and interventional randomized clinical trials predominantly for very low birth weight (birth weight <1500g) and other high risk neonates. NRN-led trials have evaluated new and existing therapies with the aims of improving mortality rates and decreasing morbidities of prematurity (neurodevelopmental impairment, chronic lung disease, retinopathy of prematurity) and establishing standards of care. In the 23 years since its establishment, the NRN has published > 160 reports describing morbidity and mortality outcomes, drug safety and efficacy, infection rates, consensus definitions and guidelines, predictors of outcomes, and results from randomized controlled trials. While the NRN has made significant contributions to the management of neonates, morbidity free survival of very low birthweight neonates remained unchanged from 1990–2002.(2)

Despite the research generated from established networks of NICUs, most of the published neonatal research has been generated from single-center experiences. These studies are susceptible to sample bias, reporting bias, treatment bias, decreased objective input from non-institutional investigators on study design, poor recruitment, and unreliable outcome measures.

These biases are also often present in single-center studies conducted in older patients; however, interpretations of single-center neonatal studies are crippled by large center differences in outcomes.(3) These center-differences are often 10-fold for major morbidities between similarly-sized academic NICUs. For instance, for very low birth weight infants in the centers of the NRN, the incidence of late onset sepsis ranges from 12 to 38%, the incidence of chronic lung disease from 3 to 43%, mortality, from 10 to 36%, and the incidence of invasive candidiasis for neonates < 1000 g birth weight ranged from 2 to 20%.(4)

A striking example of trial design and use of single-center data relates to fluconazole prophylaxis. In a single-center trial of fluconazole to prevent invasive candidiasis in neonates <1000g birth weight, investigators reported an absolute decrease of 20% (20% vs. 0%).(5) The national median incidence of invasive candidiasis in neonates <1000g is 7%, 3-fold less than

that reported in the single center trial; moreover, the baseline incidence in countries outside the United States is 1–5%. For the investigator who seeks to design pharmacokinetic or therapeutic trials for invasive candidiasis, the primary inclusion criteria or primary endpoint may be easily achievable or hopelessly impractical depending upon sites in which the trial is conducted.

In all patient populations, the reliability of trial results cannot be determined without knowing the incidence of the disease of study at the site where the trial is conducted; however, in neonatology this admonition is supported by striking center-difference data. While smaller investigator-initiated neonatal trials make significant contributions to clinical practices, results should be interpreted with caution. Sample size calculations, primary outcome analysis, sample selection, and statistical measurements are especially important with single institution trials.

Uncommon adverse outcomes are difficult to identify in multicenter trials and nearly impossible to identify in single center trials. A trial with 80% power to detect a difference in serious adverse events for a therapy that causes a 1% increase in serious adverse events over baseline requires 1280 subjects.

For a trial to provide sufficient power to detect significant differences in a particular treatment response, the incidence of disease at participating sites should be representative of the median incidence in most NICUs. Centers with a high incidence of certain clinical outcomes often report positive study results when they report the results from their own center or lead enrollment in multicenter trials. These studies often report a low number needed to treat for the intervention. However, the same intervention in a lower incidence center may require exposure of the therapy to hundreds of patients to prevent one adverse outcome.

Interventions with demonstrated efficacy in a high incidence setting may therefore have a negative risk-benefit ratio in lower incidence centers. If an intervention decreases the risk of an adverse outcome by 80%, the numbers needed to treat to prevent 1 adverse outcome for institutions with a baseline rate of 25%, 10%, 3% and 1% are 5, 12, 167, and 500, respectively. Investigators should use large numbers of centers whose overall incidence of the outcome of interest reflects the incidence of most NICUs, otherwise conclusions from the trial may not be broadly applicable.

Clinicians typically design and participate in studies related to problems important to their patients. Given the striking center-differences, the clinical studies in the nursery have most often been conducted in a few nurseries with extremely high incidence of disease. The observed reductions in disease have led several authors to conclude that those of us in the mainstream (lower incidence settings) should adopt widespread use. This phenomenon results in the paradox that although prophylaxis (or therapeutics) may be effective where it is studied (the high incidence setting), these interventions should not necessarily be adopted by all (low and moderate incidence) units. The cause of the paradox is an example of sample selection bias: sites that participate and often lead enrollment in studies are the high incidence sites that naturally view the problem under study as a public health threat. Resolution of the paradox is the conduct of simple trials with a large number of centers whose median incidence of disease reflects the broader community.

Potential Lessons Learned for Cooperative Groups in Neonatology

In the United States, 95% of children with cancer are seen at a COG institution, and 60% of eligible children will be enrolled in at least one trial; incredibly, 90% of eligible children with cancer <5 years of age are enrolled in at least one trial.(1) This approach is essential to improve outcomes for rare oncology diseases. The pediatric oncology experience can serve as a model for improving quality and consistency across NICUs and characterizing neonatal

pharmacology. Enrolling the majority of neonates <1000g in studies by expanding the number of sites participating in neonatology trials is the best way to move forward. Enrollment of infants in well-designed multicenter studies within the context of a research consortium will result in a broader representation of diverse NICU practices and lead to standardized evidence-based treatment that will reduce neonatal morbidity and mortality.

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