Request for INRG Data Analysis

Proposal Title: Evaluation of the Effect of Trial Participation on Outcomes for Intermediate and High-Risk Neuroblastoma Patients

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Specific Aims:
Clinical trials allow for groundbreaking advancements in care, leading to new treatment options and superior survival outcomes. Participants in clinical trials may benefit by gaining access to otherwise unavailable treatments and tight adherence to best practices per study requirements may also impart a survival benefit, even for those assigned to standard of care. In a pan cancer analysis, adult oncology patients who participated on clinical trials had lower cancer-specific mortality than the generally oncology population (HR 0.74; 95% CI 0.66–0.83).¹ Many providers assume this is also true in neuroblastoma, but this has yet to be demonstrated in a statistically rigorous manner. Sociodemographic factors can influence a family’s decision to participate in a clinical trial and it is unclear how these factors have impacted neuroblastoma trials and if this may contribute to the worse outcomes seen in African Americans.² To better understand the effect of trial participation on outcome and how patient demographic factors may influence trial results, we propose to analyze intermediate- and high-risk neuroblastoma patients as a whole and stratified by risk group to determine if enrollment on a clinical trial is associated with improved event free (EFS) and overall survival (OS), irrespective of assigned treatment arm. In the INRGdb, there are 6,400 Children’s Oncology Group (COG) patients with known survival outcomes who are likely intermediate- or high-risk and diagnosed between 1991 and 2016. Of these, there are approximately 2,000 intermediate or high-risk patients on clinical trials and 4,400 on biology studies. This project has potential to inform both providers and families regarding the utility of clinical trial participation and elucidate potential disparities in therapeutic trial participation rates. The Specific Aims of this study are:

1. To investigate whether neuroblastoma patients enrolled on clinical trials have improved EFS and OS compared to those enrolled on biology studies in the cohort of approximately 6,400 intermediate and high-risk COG patients in the INRGdb.
2. Determine associations of demographics, clinical phenotype, and tumor biology with clinical trial participation and to what extent these differences may have impacted outcomes.

Hypothesis:
We hypothesize that neuroblastoma patients enrolled on clinical trials will have improved EFS and OS compared to those of patients not enrolled on a trial. Even for patients treated with standard of care on study, a strict adherence to protocol is associated with higher quality of medical care and improved outcomes. We further hypothesize that non-Caucasian patients will have lower clinical trial participation rates than Caucasians and that this may account for part of the disparities in outcomes between these groups.

Patient Cohort (Eligibility Criteria):
All patients enrolled at diagnosis on an intermediate- or high-risk Children’s Cancer Group (CCG), Pediatric Oncology Group (POG), or COG study with known outcomes will form the trial cohort. While outcomes are not currently available from patients enrolled on ANBL0531, we
anticipate that the main manuscript form this trial will be published shortly and we plan to incorporate those patients in our analysis. The control cohort will consist of intermediate- or high-risk patients enrolled only on biology studies with known outcomes. Risk stratification of the control cohort will be determined as described and we will exclude low-risk patients. Only patients with the known sociodemographic data will be eligible for specific aim 2.

Background:
Clinical trials have led to an increased likelihood of survival for cancer patients and most pediatric oncologists believe clinical trials offer the best treatment for their patients. When patients are enrolled on clinical trials, they are more likely to receive intensive monitoring and stay more adherent to treatment protocols. Clinical trial patients, including those receiving the standard of care, receive more frequent evaluations than non-trial participants. However, it is also known that other factors, such as socioeconomic status or predefined eligibility criteria, may influence the survival outcomes in these studies.

Neuroblastoma treatment in the 1970s and 1980s consisted of a combination of chemotherapy, surgery, and radiation therapy. Over time, treatment has evolved to be tailored to the level of risk of relapse and death for each neuroblastoma patient. Patients classified as intermediate-risk have relatively excellent outcomes, and current non-randomized study approaches are attempting to reduce therapy for these patients. The POG 9243 study established the potential for therapy reduction for intermediate-risk patients with MYCN-nonamplified, diploid tumors. The COG A3961 study demonstrated the effectiveness of combination therapy followed by surgery to increase survival rates with patients receiving either four or eight rounds of chemotherapy depending on histology and response. Patients had a 3-year OS of 96% compared to 90%-95% historically, serving as an example of increased survival rates enabled by clinical trials. COG ANBL0531 was designed to further reduce therapy in intermediate-risk patients with favorable biology by decreasing the number of chemotherapy cycles.

While randomized clinical trials have helped improve outcomes for high-risk neuroblastoma patients, long-term survival rates remain near 50%. The CCG 3891 study established myeloablative chemotherapy with autologous bone marrow transplantation (ABMT) and subsequent treatment with 13-cis-retinoic acid (cis-RA) improved survival outcomes. The high-risk trial A3973, which ran from 2001 to 2006, studied the benefits of purged versus non-purged peripheral blood stem-cell transplantation though no difference was identified between treatment arms. In ANBL0032, patients randomized to receive dinutuximab, aldesleukin, sargramostim, and cis-RA had an improved 2-year OS compared to those who had cis-RA alone, though the long-term outcomes are yet to be published. Outcomes continue to improve with tandem transplant on the ANBL0532 study. Despite the success of these trials, participation carries risk and the experimental element can worry families. For a variety of reasons, many patients are treated off study and it is unclear how these patients compare to those that took part in these landmark trials. Furthermore, we do not know to what extent outcomes may have differed between patients treated on or per protocol. Thus, there is a gap in knowledge that this study attempts to bridge by evaluating if patients enrolled on clinical trials have a survival advantage, irrespective of assigned therapeutic arm.

Another concern with clinical trial results are the well documented disparities in trial participation according to sociodemographics. Minority groups, the elderly, and women have all been shown to have lower participation rates in oncology trials. Overall adult trial participation increased significantly from 1996 to 2002, yet the participation of minority groups declined. Recognizing how these disparities impact the generalizability of oncology clinical trials, the IOM and NCI have made improved recruitment of underrepresented populations a priority.
neuroblastoma, Native American and black patients have been shown to have worse survival outcomes compared to Caucasians. These groups were found to be high-risk more often, suggesting a possible resistance to chemotherapy or demonstrating a lack of access to superior healthcare. Gender disparities in clinical trial participation rate and survival outcome is influenced by which sex is affected more often by that disease. For unclear reasons, neuroblastoma impacts males slightly more often than females and it is not well studied if neuroblastoma trial participation varies by sex. Participation disparities may lead to issues with study generalizability that may impact treatment advances for patients. Thus, it is important to investigate potential disparities in neuroblastoma in order to inform future efforts in trial recruitment.

**Significance:**
This project will enhance physician, patient, and family understanding of the value of therapeutic clinical trial participation for neuroblastoma patients. Clinical trials are often perceived by families to be a risky proposition, though participation rates remain high, in part because many families feel a sense of altruism during the stressful time around diagnosis. This research will further our understanding of the impact of clinical trials, not just as a means of improving outcomes for future patients, but also for participants receiving standard of care. If this study shows that trial participants have improved outcomes regardless of treatment arm, practitioners and families will likely have greater incentive to participate in future investigations. Helping to reduce the fear of trial participation by demonstrating overall effectiveness may help to increase clinical trial participation among all populations and therefore help the advancement of neuroblastoma treatment. Furthermore, providing knowledge to physicians and families on sociodemographic gaps in trial recruitment may help to improve the generalizability of future neuroblastoma trials.

**Proposal Description:**
We will perform an analysis of outcomes according to participation in clinical trial enrollment status, data which have recently been incorporated into the INRG. We will limit our analysis to COG patients as this is the only consortium to provide clinical trial enrollment to the INRG. Based on the dates of enrollment of COG trials for intermediate- and high-risk patients, we will evaluate patients diagnosed between 1991 and 2016, ensuring at least three years of survival outcome. Using the INRG Cohort Discovery tool, we estimate there are 10,700 patients in the INRGdb diagnosed in this time period. This is excluding approximately 400 patients from ANBL0531 for whom outcome data should be available in the coming months. Assuming that approximately 20% of neuroblastoma patients are intermediate-risk and 40% are high-risk, there should be roughly 2,100 and 4,300 patients in each risk group with known outcome, respectively. We anticipate identifying 262 patients from POG 9243, 479 from A3961, and 464 from ANBL0531. Thus, we expect a cohort of approximately 1,200 intermediate-risk patients who were enrolled on trials and 1,300 patients not enrolled on clinical trials. The Cohort Discovery tool identified 452 patients on trial 3891 and 318 patients on A3973, totaling 770 high-risk patients on trials. We expect approximately 3,500 high-risk patients not on clinical trials to be in the database. For aim 2, we the Cohort Discovery tool suggests that 90% of patients in the analytic cohort will have complete sociodemographic data for analysis.

Patients will be analyzed as a whole and by risk group according to three strata: 1) patients on an experimental arm, 2) patients on a control arm, 3) and patients not on a clinical trial. These data will be used to create Kaplan-Meier curves for EFS and OS with respect to trial participation, risk group, and treatment era. We will analyze the patients on the experimental and control arms compared to the patients not on trial. Because treatments have changed over time, our primary analyses for high-risk patients will be restricted to the periods during the CCG
3891 and COG A3973 trials (Table 1). Primary analyses for intermediate risk patients are described in Table 2. Additionally, we will analyze the patients on the treatment arm of positive studies versus the patients not on trial at later time points to further determine being treated on a study contributes to improved patient outcomes. Differences between patient and tumor factors between groups will be assessed by t-tests or chi-squared tests as appropriate. Multivariate analysis will be performed using Cox regression to assess the impact of sociodemographic factors such as sex, age, and race. We will also account for the evolution of treatment over time as experimental arms become standard of care by incorporating treatment era into our models. If we identify that patients have comparable or improved outcomes when participating on clinical trials, families may have a greater incentive to enroll on trials in the future. This proposed analysis will provide information on the generalizability of clinical trials in neuroblastoma patients, ultimately helping to advance treatment options and improve outcomes for neuroblastoma patients.

**Data Requested:**
Patient characteristics, diagnostic information, outcomes, clinical trial or biology study enrollment and treatment arm, and all potential biologic risk factors for all patients treated on COG protocols for patients diagnosed between 1991 to 2016.

**Collaborating Biostatistics:**
Sang Mee Lee, PhD

**Literature Cited:**


21 Clegg, L. X. et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results:


