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Physician and Nurse Beliefs of Phase I Trials in Pediatric Oncology

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Abstract

Background—In order to improve the survival of children with cancer, novel therapies must be identified. Promising agents are tested in Phase I trials in order to identify appropriate dosing and describe toxicity in children. The identification and referral of candidate patients for Phase I trials relies heavily on medical providers who must balance their own perceptions of Phase I trials with the desires and willingness of the patient and his/her family.

Objective—The goal of the present study was to evaluate and compare physician and nurse perceptions regarding the beliefs, expectations, and perceived benefits of Phase I clinical trials.

Methods—A survey consisting of 21 questions was sent to 419 physicians and nurses practicing pediatric oncology at 30 different institutions. With the exception of 10 demographic questions, items were either rank ordered or rated on 5-point Likert scales.

Results—Ninety-four physicians and 122 nurses completed the online survey. Physicians and nurses differed in their knowledge of the goals and medical effects of Phase I clinical trials.

Conclusions—Physicians and nurses hold positive beliefs regarding Phase I clinical trials and support their role in the treatment of children with cancer. Education is necessary to increase nurses' knowledge of the goals and outcomes.

Implications for Practice—These findings suggest that continued education of nurses as well as physicians about the goals, execution, and monitoring of Phase I therapy would be worthwhile.

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Phase I clinical trials in pediatric oncology are the important first step in the evaluation of new treatment regimens for childhood cancer and offer potential treatment for patients for whom all standard therapies have failed. The development and completion of phase I clinical trials is vital to the continued improvement in survival rates for childhood cancers. While phase I trials in pediatric oncology are safe and relatively well-tolerated^{1,2}, the decision to enroll a child on a phase I study can be a complex decision for families³. Research indicates that families' decisions to enroll their child on a phase I clinical trial are heavily influenced by the opinions of those around them, especially in regards to medical providers^{4,5}. As such, it can be expected that physician and nurse beliefs and expectations concerning phase I clinical trials may modify the recommendations made to children and families.

Given these influences on family decision-making processes, it is important to understand the beliefs and expectations that medical providers hold regarding phase I clinical trials. To date little research has been conducted to evaluate provider perceptions and more specifically⁶⁻⁸, only one study has assessed attitudes of both physicians and nurses concurrently. While results indicate that a majority of physicians and nurses have a positive view of phase I trials, a significant subset report negative perceptions⁸. Additionally no studies have compared specific differences across physician and nurse perceptions, which may be important given the potential effect these patterns may have on referral recommendations and family decision-making processes.

While pediatric oncologists are responsible for recruiting and enrolling children on phase I trials, the role of nurses is also critical. The responsibilities of nurses caring for pediatric oncology patients are diverse, including serving as medical caregiver, advocate, educator, and research assistant⁷. Given the diverse functions of nurses caring for pediatric oncology patients, including the extended periods of intense face-to-face interactions, the impact that nurses have on patient and family decision-making processes is important to consider. While research is limited regarding nurses' role in phase I trial enrollment in pediatric oncology, their influence has been documented clinically with adults. In fact, there is growing literature examining their perceptions of clinical trials in regards to adult patient care. In a large study evaluating research nurses' perceptions of phase I, II, and III clinical trials, most nurses had positive views of phase II and III trials though they were less supportive of phase I trials⁸. Additionally, oncology nurses were more likely to recommend patient participation in phase III trials as compared to phase I and II trials. These findings suggest that nurses are more comfortable with trials where the main goal is to compare the effect of a promising experimental intervention with the current standard of care, as opposed to trials primarily intended to determine the safety and tolerability of a new agent. In addition, the relative lack of exposure to phase I trials among many nurses may influence perceptions and elicit biases. Interestingly, this study also analyzed factors associated with perceptions of clinical trials and, compared to physician perceptions, nurse perceptions were more strongly influenced by lack of knowledge and related training and as opposed to occupation⁸. It is possible similar patterns are true in pediatric oncology phase I trials, such that experience and training with these protocols is more important than provider occupation.

To better understand medical care providers perceptions of phase I trials in pediatric oncology, the goal of the present study was to evaluate and compare physician and nurse beliefs, expectations, and perceived benefits of pediatric oncology phase I clinical trials.

Method

Participants

Participants were 94 pediatric oncologists and 122 pediatric nurses practicing at 30 different randomly selected COG member institutions in the United States (for list of institutions email first author). Inclusion criteria required that participants be practicing within the field of pediatric oncology at a COG member institution.

Survey Procedure

The University of Alabama at Birmingham institutional review board approved the study and waived the requirement for documentation of informed consent. To recruit participants, a random sample of 15 phase I consortia institutions and 15 non-phase I consortia institutions were selected from the list of member institutions available on the COG website. Phase I consortia included the COG Phase I/Pilot Consortium, Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL), Pediatric Brain Tumor Consortium (PBTC), Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC), and New Approaches to Neuroblastoma Therapy (NANT). Pediatric oncologists and nurses were sent an email including a description of the survey and an invitation to participate. The email included a link to the web-based questionnaire. An email reminder with the survey description and link was sent two weeks following the original invitation. Participant flow is illustrated in the Figure titled Consort Flow Diagram. The final sample consisted of 94 physicians and 122 nurses.

Survey Development

The survey was developed for this study by the investigators (see supplemental material for full copy). Survey content was based on previous exploratory work assessing providers' perceptions of phase I trials⁶. A draft survey was prepared and subsequently modified after pilot testing with a sample of pediatric oncology physicians and fellows from the investigators' institution as well as experts in the field. The final survey consisted of 21 items. Ten demographic questions assessed participant age, gender, ethnicity, oncology experience, professional responsibilities, and experience with patients referred to or enrolled in phase I trials. The remaining 11 questions assessed beliefs about phase I trials including treatment decisions, enrollment, potential benefits/risks, and ethical issues. With the exception of the demographic questions, items were either rank ordered or rated on 5-point Likert scales.

Analytic Strategy

Given the lack of data concerning pediatric oncologists and nurse perceptions of phase I trials, the primary objectives of the study were to generate descriptive data about medical providers' beliefs concerning phase I clinical trials. Comparisons were made between physicians and nurses. For continuous variables, t-tests were used to evaluate group

differences. For all ranked and rated data, chi-square tests were used to evaluate differences in the distribution of responses for each group.

Results

Respondents

Demographic information is presented in Table 1. Physicians and nurses did not differ on age, ethnicity, years of pediatric oncology experience, or experience with children on phase I studies. As expected, physicians were more likely to be male compared to nurses.

Knowledge of Phase I Clinical Trials

Responses to questions assessing provider knowledge of phase I clinical trials are shown in Table 2. Physicians were more likely to correctly identify the main goals of phase I studies including testing the safety, determining the maximum tolerated dose (MTD), and identifying the dose-limiting toxicity (DLT) of an experimental drug. In addition to being less likely to correctly identify the main goals of phase I trials, nurses were more likely to incorrectly endorse goals including determining the efficacy of a drug for a specific disease and extending the lifespan of a patient. No providers endorsed curing patients as a goal of phase I therapy.

Beliefs of Phase I Clinical Trials

Provider beliefs about phase I clinical trials are presented in Table 3. The vast majority of physicians and nurses indicated that future children diagnosed with cancer would benefit from phase I clinical trials and that trials did not have a negative impact on children's quality of life. Physicians and nurses differed on some aspects of their beliefs with physicians being less likely to endorse the belief that families understand the goals of and have realistic expectations for phase I trials. Consistent with these findings, physicians were more likely to report that consent forms are difficult for families compared to nurses. Regardless, both groups agreed that children who are old enough to consent for treatment can make treatment decisions. Finally, despite perceptions of difficulty with consent and family understanding, less than half of physicians and nurses believed that phase I trials offered false hope for patients and families.

Enrollment Rationale

Provider questions assessing families' motivations for enrolling on phase I clinical trials are shown in Table 4. The number one reason physicians and nurses believed families enroll on phase I clinical trials is to keep hope alive. In line with the belief that families will choose to enroll on phase I studies as opposed to stopping treatment, providers also rated that families want more treatment as a top reason for enrolling though nurses were slightly more likely to endorse this as a reason compared to physicians. Nurses were less likely to believe that families enrolled on phase I trials out of guilt compared to physicians, however this was not a primary reason for enrolling for either group.

Medical Outcomes

Provider' estimates of the potential medical benefits and toxicities experienced by children enrolled on phase I clinical trials were variable. Nurses were more likely to estimate that a higher proportion of children would experience medical benefit compared to physicians. In contrast, all physician participants believed that less than 40% would experience medical benefit. In regards to toxicities, the majority of nurses estimated that between 80 and 100% of children would experience significant toxicities or adverse events from phase I trials; while majority of physicians believed that less than 40% of children would experience significant toxicities or adverse events ($p < .001$).

Discussion

Results of the present study suggest that physicians and nurses differ in their level of understanding of phase I clinical trials with physicians showing a greater level of knowledge regarding the primary goals of these trials. In regards to medical outcomes, nurses were more likely to overestimate the toxicities and underestimate the medical benefits associated with phase I clinical trials. Physician responses were more accurate in medical outcome estimations, supported by recent research indicating that phase I trials have demonstrated a historical objective response rate of 6.8% for single agent trials and 20.1% for trials of multiple agents². Toxicity has historically been low in phase I trials with only 24% of patients experiencing a DLT and a drug-related death rate of only 0.5%². Interestingly, despite differences in nurse and physician knowledge of phase I goals, perceptions of toxicities, and estimation of benefits, nurses were more likely than physicians to believe that families understand the goals of phase I trials and have realistic expectations for outcomes and they were less likely to endorse that consents forms are difficult to understand for families. More research is needed to evaluate why nurses, despite endorsing more negative perceptions of phase I trials compared to physicians, believe that families are knowledgeable and aware of phase I trial purposes and outcomes.

Despite these differences in knowledge and perception of phase I trials, physicians and nurses generally supported the beliefs that future children diagnosed with cancer would benefit from phase I clinical trials, and that trials did not have a negative impact on children's quality of life. Both groups did acknowledge however that families need increased support during this stage of the cancer journey. It is possible that, despite differences in specific understanding of phase I trials, physicians and nurses who care for children on phase I trials on a regular basis are exposed to both the positive and negative aspects and therefore may have more realistic beliefs regarding the impact of these trials on the lives' of children and families outside of the medical arena.

These findings have important implications in regards to the execution of phase I clinical trials and the care of children and families enrolled on these studies. First, as nurses play an ever-increasing and integral role in the care of pediatric oncology patients⁹, it is important to recognize the impact they have on children and families' treatment-making decisions. Increasing efforts to educate nurses regarding the goals and treatment-related outcomes (e.g. medical benefit, QoL, toxicity) of children enrolled on phase I clinical trials may in turn effect the way nurses interact and influence families considering phase I therapy. Currently

no standard educational requirements regarding experimental studies exist for medical providers. Education concerning phase I clinical trials therefore likely varies across institutions, occupations, and individual interests, and must be taken into consideration when evaluating provider perceptions and knowledge. Institutions participating in these trials or who frequently provide care for children enrolled on these studies may consider in-service workshops or seminars geared toward providers working with these populations.

Taken as a whole, the present study provides insight into the perceptions and beliefs of pediatric oncologists and nurses regarding phase I trials. These findings suggest that continued education of physicians as well as nurses about the goals, execution, and monitoring of phase I therapy is important. Methods to improve the consent process may also be necessary to better inform patients and their families.

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Figure.
CONSORT Flow Diagram

Table 1

Participant Characteristics (N = 94 Physicians; N = 122 Nurses)

Variable	Physician	Nurses
	[M(SD) or %]	
Gender (% Male) ^a	56%	1%
Age (years)	45.59 (9.04)	40.69 (9.41)
Ethnicity (% Caucasian)	87%	93%
Years of Pediatric Oncology Experience	13.96 (9.28)	13.74 (8.51)
Cared for Child on Phase I Study (% yes)	65%	70%

^a indicates significance at $p < .05$.

Table 2

Knowledge of Phase I Clinical Trial Goals

Variable	Physicians	Nurses
Determine efficacy of drug in disease treatment ^b	1.0%	20.9%
Test safety of experimental drug^b	89.7%	58.3%
Cure patients of disease	0%	0%
Determine safe dosage range^a	92.8%	80.0%
Extend lifespan of patient ^a	2.1%	13.0%
Identify side effects of experimental drug^b	88.7%	59.1%

Note. Values represent the percentage of respondents who endorsed the statement as a goal of Phase I clinical trials. Bolded statements reflect true goals of Phase I clinical trials.

^a indicates significant χ^2 at $p < .01$,

^b indicates significant χ^2 at $p < .001$.

Table 3**Beliefs about Phase I Clinical Trials**

Variable	Physicians	Nurses
Drugs given to patient with therapeutic intent	64.6%	55.6%
Patients benefit from participating	54.7%	48.7%
Families benefit from child's participation	67.8%	55.7%
Future children diagnosed with cancer benefit	97.9%	96.5%
Consent forms are difficult ^a	76.0%	59.2%
Families understand goals ^b	24.7%	50.4%
Families have realistic expectations ^a	16.5%	35.6%
Families need increased support	67.7%	73.0%
Families will choose Phase I over stopping	58.4%	63.5%
Children of age can make treatment decisions	72.1%	67.0%
Parents should make treatment decisions	45.8%	48.7%
Have negative impact on child's QOL	10.4%	17.4%
Offer false hope for parents	44.8%	37.7%
Offer false hope for patients	35.4%	30.4%

Note. Values represent the percentage of respondents who agreed or somewhat agreed with the survey question.

Abbreviations: QOL, quality of life.

^a indicates significant χ^2 at $p < .05$,

^b indicates significant χ^2 at $p < .001$.

Table 4

Perceptions about Families' Decision-Making Rationale for Enrollment on Phase I Clinical Trials

Variable	Physicians	Nurses
Reasons for Enrolling ^a		
Want to keep hope alive	47.3%	37.7%
Want more treatment ^b	18.9%	25.0%
If they don't, they will feel guilty later ^b	8.5%	3.8%
Cannot accept death/fear of losing child	12.9%	17.6%
It was offered	7.4%	8.2%
Want to help other children with cancer	4.2%	3.8%

^a Values represent the percentage of respondents who selected the reason as the number one reason for enrolling on a phase I clinical trial.

^b indicates significant χ^2 at $p < .05$.