Communicating and Understanding the Purpose of Pediatric Phase I Cancer Trials

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A B S T R A C T

Purpose

Quality informed consent should provide a clear understanding of the purpose of the research. Given the ethical challenges of pediatric phase I cancer trials, it is important to investigate physician-parent communication during informed consent conferences (ICCs) and parental understanding of the purpose of these studies.

Methods

In the multisite Informed Consent in Pediatric Phase I Cancer Trials study, 85 ICCs for phase I research between June 2008 and May 2011 were directly observed, and 60 parents were subsequently interviewed. The scientific purpose was defined as composite understanding of drug safety, dose finding, and dose escalation. We determined the frequency with which physicians explained these and other phase I-related concepts during the ICC. Parent interviews were analyzed to determine understanding.

Results

The child was present at 83 of 85 ICCs. Only 32% of parents demonstrated substantial understanding of the scientific purpose of phase I cancer trials; 35% demonstrated little or no understanding. Parents of higher socioeconomic status and racial majority status were more likely to understand the scientific purpose. Factors associated with understanding included physician explanation of the goal of the applicable phase I protocol offered (explained in 85% of ICCs) and explanation of the dose cohorts (explained in 43% of ICCs). Physicians explained drug safety in 23% of ICCs, dose finding in 52% of ICCs, and dose escalation in 53% of ICCs.

Conclusion

Many parents of children participating in phase I trials do not understand the purpose of these trials. Physician-parent communication about the purpose of phase I research is lacking during ICCs.

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INTRODUCTION

Clinical trials have identified many effective therapies for childhood cancer.¹ When standard treatment has failed or is not available, children may be eligible for phase I trials. These studies offer minimal prospect of direct benefit²; it is highly unlikely that a phase I drug will cure a child.³ The purpose of phase I research is not to assess the efficacy of an anticancer drug but to establish the safe, appropriate dose for subsequent phase II trials. To find a safe dose for phase II efficacy trials (ie, maximum-tolerated dose [MTD]), the drug dose is escalated in a series of enrolled cohorts of patients until the dose-limiting toxicity (DLT) is defined.⁴

If parents are to make a truly informed decision about their child's participation in phase I research,

they must understand the scientific purpose of the study⁵ because individual risks associated with study participation may well outweigh benefits.⁶ However, research on pediatric clinical trials, like that in adult oncology,⁷⁻⁹ has demonstrated deficiencies in parental understanding of research-related topics^{10,11} and prognosis.¹² The phenomenon of therapeutic misconception, a belief that the primary goal of research is to benefit the participant,¹³ further complicates informed consent. Physicians report that it is challenging to communicate research objectives and alternatives to parents while also conveying hope.^{14,15} Given the complexities of informed consent, researchers have called for empirical examination of communication between physicians and families about pediatric phase I cancer trials.^{16,17} The study of physician-parent

communication and high-quality informed consent is ethically significant in view of the long-standing concerns and controversy about medical research involving children^{5,18} and the low likelihood of medical benefit in phase I research.¹⁹

To our knowledge, physician-parent communication and parental understanding of the scientific purpose of phase I research have not been examined. This study assessed physician-parent communication and parental understanding of the scientific purpose of pediatric phase I cancer trials by directly observing informed consent conferences (ICCs) and subsequently interviewing parents. Physician explanations of DLT, MTD, and dose escalation were compared with parental understanding of the scientific purpose, which was defined by parents' summed understanding of drug safety, dose finding, and dose escalation. We also examined physician explanation of additional phase I-related topics and parent- and ICC-related correlates of parental understanding.

METHODS

Recruitment and Study Procedures

This study was conducted at six hospitals with active pediatric phase I trials and was approved by institutional review boards at each site and the coordinating site. English- and Spanish-speaking families considering participation in an open phase I pediatric (age 0 to 21 years) cancer trial were eligible. Eligible families were identified by trained research assistants (RAs) via electronic medical record review and through consultation with medical staff. Before the ICC, RAs obtained consent from physicians, parents, and patients age 18 years or older and assent from patients age 7 to 17 years. Eighty-five families agreed to observation and audio recording of ICCs regarding phase I research; 21 families declined. RAs made every attempt to attend and record all meetings in which phase I research was discussed. Of the 85 ICCs, 26 ICCs included two separate recorded meetings and four ICCs involved three meetings. Of the 85 participating families, 60 agreed to a subsequent interview, which occurred on average 5.6 days (range, 0 to 25 days) after the ICC. In each of the 60 families, the parent most involved in the ICC as determined by the RA was interviewed. Reasons for not participating in parent interviews included declining health of the child ($n = 5$), ineligibility for phase I trial after ICC ($n = 5$), passive refusal ($n = 12$), and inability to contact ($n = 3$).

Outcome Measures

Demographics. Parents provided the following demographic data during the interview: parent and patient age, sex, education, occupation, race/ethnicity, and religious preference. Socioeconomic status (SES) was calculated by using the Hollingshead Index of Social Position,²⁰ which combines occupation and education. A lower score indicates higher SES. Parents reported whether their child had previous clinical trial experience. Physician demographic and practice data were also collected.

Codebook. The codebook used in previous studies^{10,21} was modified for use in the phase I context. In the recorded ICCs, physician explanation of the following six phase I-related concepts was coded and evaluated: drug safety (DLT), dose finding (MTD), dose escalation, dose cohorts, goals of the applicable phase I protocol (although all phase I trials are dose-finding trials, some drugs have different mechanisms of action, or studies may have specific pharmacokinetic and pharmacodynamic end points), and study drug dosage would not be increased for an individual patient.

Coders were trained in identification and coding of the communication topics. Thirty percent of the conversations were coded by two individuals to assess inter-rater reliability. κ scores for the six physician-explained concepts ranged from 0.77 to 1.0.²²

Parent Interviews. Interviews with one parent from each family were conducted by the RA. The instrument was adapted from those used in our previous research¹⁰ and pilot tested for the phase I context. Interviews were recorded, transcribed, and consensus coded to determine parental understanding.

Parental understanding of the scientific purpose of phase I research was assessed by using four questions similar to a subset of phase I-related questions included on the Quality of Informed Consent Questionnaire,²³ which was designed according to federal regulations concerning human subjects research and recommendations from the National Cancer Institute's Working Group on Informed Consent.^{9,23,24} For example, to elicit parental understanding of drug safety and dose finding, parents were asked the following questions: "Could you tell me, in your own words, what this [trial] consists of?" "What are the scientific goals of this [trial]?" To assess understanding of dose escalation, parents were asked the following questions: "What sorts of treatment will your child get if you decide to participate in this [trial]?" "If your child enrolled in this [trial], how will the dose of the new medicine your child receives be decided?"

Responses to these post-ICC interview questions were reviewed, and parents received a score of no understanding (0.0), partial understanding (0.5), or substantial understanding (1.0) for each of the three concepts (drug safety, dose finding, and dose escalation) used to determine parental understanding of the scientific purpose. Parents were considered to understand drug safety if they conveyed that the trial's purpose was to identify the toxicities/adverse effects of the drug. They were considered to understand dose finding if they conveyed that the trial sought to find the dose to be used in phase II trials and/or determine the highest safe drug dose. Parents were considered to understand dose escalation if they conveyed that each consecutive group of patients enrolled receives a higher drug dose than the previous group. The three concept scores were summed to generate a composite understanding score of the scientific purpose of phase I cancer trials.

Statistical Analysis

Descriptive statistics are presented as means and standard deviations (SDs) for continuous variables and as percentages and cell sample sizes for categorical variables. Variables associated with parental understanding were examined by χ^2 statistics for categorical variables and by t tests for continuous variables. For the dichotomous summary variable of composite understanding, partial understanding (score, 1.0 to 1.5) and substantial understanding (score, 2.0 to 3.0) groups were combined and compared with the no understanding (score, 0.0 to 0.5) group. Because of occasional small cell sizes, exact χ^2 statistics were computed for all analyses. Both P values and effect size are provided for each variable associated with the composite understanding score. Because our *a priori* hypothesis was that physician explanation of phase I-related concepts would result in improved parental understanding, one-tailed probability tests were computed. Special emphasis was placed on identifying moderate effect sizes (differences of 20% to 25% between groups) as being clinically significant.^{22,25}

RESULTS

Patient and Parent Demographics

Patients in the sample had a mean age of 11.3 years (SD, 5.5 years). Most patients were male (63%), and the most common diagnoses were brain/CNS malignancies (33%) and bone/soft tissue malignancies (31%; Table 1). At the time of analysis, 49 of 85 patients had died; the mean time span from the ICC to death was 207 days (SD, 175 days). Parents participating in the interview were most often female (72%) and white (85%). Social position was evenly distributed.

No significant difference was found between the 60 parents interviewed and the 25 parents not interviewed in the following variables: study site, whether the patient had received care at another institution, diagnosis, role of physician (eg, attending, fellow), sex of parent most involved in ICC, enrollment onto the phase I trial, ICC duration, and number of people present in ICC. Parents of female patients (58% v 78%; $P = .055$) and younger patients (mean age, 8.1 v 12.3 years; $P = .015$) were less likely to participate in parent interviews than those who did agree to be interviewed.

Table 1. Patient and Parent Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No.	%
Patients, n = 85		
Age, years		
Mean	11	
Range	1-12	
Sex		
Male	54	63
Female	31	37
Cancer diagnosis		
Brain and CNS	28	33
Bone and soft tissue (sarcoma)	26	31
Neuroblastoma	17	20
Leukemia	7	8
Other	7	8
Days from ICC to patient death*		
Mean	207	
Range	25-763	
Parents, n = 60		
Age, years		
Mean	42	
Range	23-66	
Sex		
Male	17	28
Female	43	72
Race/ethnicity		
Non-Hispanic white	51	85
Other	9	15
Index of Social Position†		
1-2	19	32
3	20	33
4-5	21	35

Abbreviation: ICC, informed consent conference.

*N = 49 at the time of analysis.

†Lower scores are representative of higher socioeconomic status.²⁰

consent document in 59 observed ICCs, and a parent signed the document during the ICC in 56 ICCs. Parents asked an average of 15.6 research-related questions.

Physician-Parent Communication During ICCs

Physicians explained drug safety (DLT) in 23% of ICCs, dose finding (MTD) in 52% of ICCs, and dose escalation in 53% of ICCs. They explained dose cohorts in 43% of ICCs and the goal of the applicable phase I protocol in 85% of ICCs. The fact that a patient's dose would not be increased was conveyed by physicians in 8% of ICCs. Overall, parent SES and race/ethnicity were not associated with physician explanation of the six concepts.

Parental Understanding

Parents most frequently comprehended dose finding (MTD), with 53% of parents demonstrating substantial understanding (Table 2). The least understood concept was dose escalation, of which only 12% of parents demonstrated substantial understanding. However, parents who read parts of the consent document during the ICC, as observed by the RA, were more likely than others to understand dose escalation ($\chi^2 = 5.04, P < .05$). Overall, 35% of parents demonstrated no understanding of the scientific purpose of phase I cancer trials, as determined by a lack of understanding all three concepts (drug safety, dose finding, and dose escalation).

Factors Associated With Parental Understanding

Parent racial/ethnic minority status and low SES were associated with lower understanding scores, whereas physician explanations of cohorts and trial aims were associated with higher understanding scores (Table 3). Figure 1 shows 60 cases from our study, rank ordered for physician explanation, in which parental composite understanding scores are plotted. In 37 cases, physician explanation equaled or exceeded parental understanding. For example, in case 40, the physician explained two of the three concepts, but the parent did not understand any of them. In 23 cases, parent understanding surpassed physician explanation. Physician explanation of all three concepts was not found to be associated with a high level of understanding ($P = .71$). However, physician explanation of dose cohorts in the study design was associated with greater parental understanding of the scientific purpose. A clinically significant relationship was seen between physician explanation of the goal of the applicable trial and parental understanding of the scientific purpose. The effect sizes observed support these findings; three of four variables seen in Table 3 reflected

Physician and ICC Characteristics

Physicians had a mean age of 44 years (SD, 6.8 years) and had cared for children with cancer for approximately 14 years (SD, 8.1 years). Most physicians were female (54%), and 15% were minorities. Attending physicians led 93% of ICCs, and a nurse was present at 40% of ICCs. Mean ICC duration was 45 minutes (SD, 20 minutes), and an average of five people (SD, 1.2 people) were present at the ICC. The patient was present at 83 of 85 ICCs, and 95% of patients were enrolled onto the study. The physician provided families with an informed

Table 2. Parental Understanding Scores (N = 60)

Concept	No Understanding		Partial Understanding		Substantial Understanding	
	No. of Parents	%	No. of Parents	%	No. of Parents	%
Individual concept						
Drug safety	32	54	5	8	23	38
Dose finding	24	40	4	7	32	53
Dose escalation	44	73	9	15	7	12
Understanding of scientific purpose, composite	21	35	19	32	20	32

NOTE. For the individual concepts, the scores were as follows: no understanding (0.0), partial understanding (0.5), and substantial understanding (1.0). The composite understanding score was computed by summing the three individual concept scores (no understanding, 0.0 to 0.5; partial understanding, 1.0 to 1.5; and substantial understanding, 2.0 to 3.0).

Table 3. Factors Associated With Understanding of the Scientific Purpose in Parents

Factor	No. of Parents (N = 60)	Partial/Substantial Understanding of the Scientific Purpose (%)	χ^2	P*	ES (%)
Minority status			4.40	.05	38
No	51	71			
Yes	9	33			
ISP score			16.91	.002	51
1-2	19	84			
3	20	80			
4-5	21	33			
Physician explanation of cohorts			8.53	.001†	36
No	34	18‡			
Yes	26	54‡			
Physician explanation of trial aim			2.79	.09†	28
No	10	10‡			
Yes	50	38‡			

Abbreviations: ES, effect size; ISP, Index of Social Position.

*All probabilities are based on exact statistics.

†One-tailed probability test. All others are two tailed.

‡Only substantial understanding was analyzed.

a large effect size, and the fourth reflected a moderate effect size.²² Previous enrollment onto a clinical trial, duration of the ICC, presence of a nurse at the ICC, study site, time elapsed between ICC and parent interview, and number of questions asked per minute in the ICC were not found to be associated with understanding.

DISCUSSION

High-quality informed consent is critically important to pediatric phase I cancer research. Of significance, only 32% of parents demonstrated substantial understanding of the scientific purpose of phase I research, which is consistent with studies that assessed understanding in adult phase I research participants.^{7,26,27} Notably, 35% of parents

Fig 1. Communication and understanding of scientific purpose. A comparison of physician explanation with parental composite understanding scores in 60 cases is shown. Explanation and understanding scores range from none (0.0) to complete (3.0). The blue shaded area indicates cases in which physician explanation equaled or exceeded parental understanding. ICC, informed consent conference.

demonstrated virtually no understanding. Further examination of physician-parent communication revealed inadequate discussion of crucial topics inherent to phase I research. Despite deficiencies in physician explanation of key concepts necessary for truly informed consent⁹ and deficiencies in parental understanding, 95% of parents enrolled their child onto the phase I trial offered.

Physician explanation of drug safety (DLT), dose finding (MTD), and dose escalation did not ensure parental understanding. Thus, persistent therapeutic misconceptions¹³ may limit parents' understanding of the scientific purpose and nature of the study. Future research should examine the degree to which patients and parents understand the risks and benefits of phase I research, alternatives to participation, and factors associated with therapeutic misconceptions, and whether parents understand that phase I trials are rarely curative and may impose significant patient burden.

Importantly, physician explanation of dose cohorts and explanation of the goals of the applicable phase I protocol were associated with greater parental understanding, pointing to ways in which physicians can improve the informed consent process and communication in phase I research. Several adult oncology studies have demonstrated the value of training physicians in such methods.²⁸⁻³⁰ Our own research demonstrates that physician training in the pediatric oncology setting increases the use of rapport-building statements³¹ and opened methods of eliciting questions in ICCs.³² Future research should consider ways in which these interventions can be modified and efficiently delivered in the phase I context. Physicians should be trained in strategies and techniques for more effectively explaining the scientific purpose of phase I research and related concepts, such as dose cohorts.

Because the mean age of patients in this sample was only 11 years, it is remarkable that the child attended 83 of 85 ICCs observed. This finding may reflect a significant cultural transformation in the way we talk to children about the life-threatening nature of their cancer. Research has demonstrated a growing consensus among parents³³ and health care providers^{34,35} supporting honest discussion with children. Future examination of young patients' perspectives on clinical research and the informed consent process may help guide researchers and regulators in developing ICC processes that ensure the appropriate involvement of children. Parents' views about the informed consent process have also yielded informative insights for improving the process and developing interventions.³⁶⁻⁴⁰ It is essential that this line of work continues to ensure that those who matter most—child research participants and their families—are heard and their concerns are addressed.

Several barriers to high-quality informed consent remain. In our study, lower SES and racial/ethnic minority status were associated with poorer parental understanding, although physician explanations did not differ in those groups. Findings emphasize the need for targeted interventions to improve the informed consent process for families of lower SES or of racial/ethnic minority status. The use of culturally sensitive support materials developed in collaboration with patients and families may facilitate understanding for these groups.⁴¹

Our findings also suggest that the ICC is not the sole determinant of parental understanding. In 23 of 60 cases, parental understanding exceeded physician explanation. Therefore, parents clearly learn about research from other sources (eg, referring physician, Internet, other parents, consent form). Future research should seek to make optimal use of these additional information sources. For example, a parent

with previous personal experience may serve as a supportive source of information for other parents considering enrollment, offering a first-hand explanation of the phase I trial that parents can easily understand. Anticipatory guidance, such as showing parents a DVD before the ICC,⁴² may also improve informed consent for phase I trials.

These results must be interpreted in light of study limitations. Although participants were recruited from six of the most active pediatric phase I research programs, these may not be representative of other programs. Because of the sample size, we only had statistical power to detect large effect sizes; however, 85 participating families is a fairly substantial sample considering that 130 to 200 patients are enrolled annually onto Children's Oncology Group phase I studies. Despite our attempt to observe and record the ICC process in its entirety, it is also possible that physicians and parents had unobserved discussions about the trial. Additionally, conversations regarding alternative options such as palliative care or hospice, as well as conversations introducing families to phase I trials, may have already taken place before the ICC. A lack of data regarding additional sources limits our understanding of information obtained outside of the ICC. Strengths of the study include direct observation of informed consent paired with follow-up parent interview, rigorous measurement of parental understanding, and a novel methodologic approach to comparing disclosure and understanding (Fig 1). This work provides a comprehensive analysis of these important conversations and the impact of communication on parental understanding.

In sum, children with refractory cancer who are recruited for phase I trials represent one of the most vulnerable populations of human study participants. Although findings show that the children are almost always present at the ICC, substantial barriers and

ethical challenges to high-quality informed consent remain. This study adds a new conceptual framework regarding the ethics of phase I cancer research that is relevant to both adults and children with terminal cancer. Results highlight the need for future examination of the role of children in phase I ICCs; of parent and patient understanding of risks, benefits, and alternatives to participation; and of interventions that can improve physician-parent communication and informed consent.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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