Ethical Issues for Control-Arm Patients After Revelation of Benefits of Experimental Therapy: A Framework Modeled in Neuroblastoma

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ABSTRACT

In 2009, the Children's Oncology Group (COG) phase III randomized controlled trial, ANBL0032, found that adding immunotherapy (Ch14.18) to standard therapy significantly improved outcomes in patients with high-risk neuroblastoma when administered within 110 days after autologous stem-cell transplantation (SCT). After careful deliberation and consultation, the COG Neuroblastoma Committee decided to offer Ch14.18 to prior trial participants who had been randomly assigned to the control arm (no immunotherapy), regardless of the time that had elapsed since SCT. This decision occurred in the context of a limited supply of Ch14.18 and no data regarding its role when administered beyond 110 days. In this article, we analyze the numerous ethical challenges highlighted by the ANBL0032 trial, including the limits of researchers' reciprocity-based obligations to study participants, post-trial access to beneficial therapies, and the balance between scientific knowledge and parental hope. These deliberations may be useful to other researchers when considering their ethical obligations to control-arm participants in the wake of a positive randomized trial.

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INTRODUCTION

Neuroblastoma is the most common extracranial solid tumor of childhood.¹ Approximately 800 new cases occur annually in the United States, with 90% occurring before age 5 years.² The clinical severity of neuroblastoma is driven by its biologic heterogeneity; nearly half of patients fall into the high-risk group.³ Despite multimodal, intensive therapy including surgery, chemotherapy, autologous stem-cell transplantation (SCT), radiation, and retinoic acid, 5-year event-free survival (EFS) for high-risk neuroblastoma has historically been less than 30%.⁴

Immunotherapy, which uses monoclonal antibodies targeting neuroblastoma-associated antigens such as GD2, is hypothesized to be efficacious in eradicating microscopic disease.^{5,6} In early clinical trials, several anti-GD2 monoclonal antibodies, including the chimeric human-mouse antibody Ch14.18, were found to be active against neuroblastoma.⁷ On the basis of these findings, a Children's Oncology Group (COG) phase III randomized controlled trial, ANBL0032, began accruing patients in October 2001 to determine if adding Ch14.18 and cytokines to standard treatment would result in improved EFS and overall survival (OS) for patients with high-risk neuroblastoma. In early 2009, a planned interim analysis of 226 eligible patients re-

vealed a significantly improved outcome with Ch14.18 plus cytokines (2-year EFS, 66% v 46% for standard therapy; $P = .0115$; 2-year OS, 86% v 75% for standard therapy; $P = .0223$). The COG Data Safety Monitoring Committee halted further random assignment,⁸ the protocol was modified, and subsequent participants were assigned to receive immunotherapy.

Therapy with Ch14.18 plus cytokines is associated with substantial burden and toxicities, including pain requiring narcotic analgesia in more than half of participants.⁸ Other serious toxicities include capillary leak syndrome, severe allergic reactions, fever, electrolyte and liver function abnormalities, low blood pressure, diarrhea, rash, and low tissue oxygen levels. Administration requires inpatient hospitalization, five courses of prolonged intravenous administration, prophylactic supportive care, and the potential for intensive care unit transfer to manage complications. ANBL0032 specified the start of delivery of Ch14.18 to be no more than 110 days after stem-cell infusion.^{9,10} There are no data supporting the efficacy of Ch14.18 when administered later than this time point, but some antibody-related adverse effects may theoretically become more severe as immune reconstitution becomes more robust with increasing time since SCT.

From the outset, the National Cancer Institute (NCI) manufactured Ch14.18 exclusively for use of COG investigators in the ANBL0032 trial. At the time of the interim analysis demonstrating its superiority, the existing supply of Ch14.18 was sufficient for only 150 patients. The COG Neuroblastoma Committee estimated that this supply would be exhausted in 12 to 18 months, even if its use was limited to current and future study participants who could be treated within 110 days of stem-cell infusion. Furthermore, a new batch of Ch14.18 was not expected from the NCI for 18 to 24 months. Because Ch14.18 was not commercially available, COG planned to keep the study active until an industry sponsor could assume responsibility for manufacturing the drug under an NCI Cooperative Research and Development Agreement.¹¹

Ch14.18 was the first new agent found to prolong survival among children with high-risk neuroblastoma in more than a decade. Accordingly, the COG Neuroblastoma Committee believed that withholding the active drug from study patients previously randomly assigned to the control arm might be ethically problematic. The committee sought input from the COG Bioethics Committee, the COG Patient Advocacy Committee, the COG group chair, and the NCI Cancer Therapy Evaluation Program. The consultative process recognized a lack of evidence regarding the efficacy of Ch14.18 when administered beyond 110 days after SCT, the serious adverse effects, and the limited drug supply. Ultimately, the committee decided that the 52 patients previously randomly assigned to the no-immunotherapy arm who were beyond 110 days from SCT and remained relapse free would be offered access to Ch14.18 if specific eligibility criteria were met. Parents who wished their child to cross over from the standard arm of the study to receive Ch14.18 were informed that access was part of ongoing research and were asked to provide a new authorization for their child. The research context and possibility that no benefit would occur were clearly stated in the crossover consent form, as follows:

“The earlier part of this study showed a strong benefit of treatment with Regimen B [immunotherapy]. That is why we are providing the option to receive treatment with Regimen B. However, we do not know if there is a benefit from the Regimen B treatment when it is started more than 110 days after transplant. It is very likely that Regimen B will not have as much benefit when it is started more than 110 days after transplant. The longer the time from transplant, the less likely it is that Regimen B will be helpful. . . . Subjects who receive treatment with Regimen B more than 110 days after transplant may be at greater risk of having adverse effects from the Ch14.18 antibody or IL2 [interleukin-2] than if they received Regimen B treatment in the first 110 days after transplant.”

In the following sections, we describe the specific questions that COG leadership and the NCI considered in coming to a final recommendation.

QUESTIONS TO BE CONSIDERED IN THE SETTING OF LIMITED SUPPLY OF A BENEFICIAL EXPERIMENTAL DRUG

The COG Neuroblastoma Committee, along with the groups it consulted, considered several ethical challenges and questions before deciding to offer Ch14.18 to ANBL0032 control-arm participants who remained progression free. First, do investigators have reciprocity-based obligations to current and prior research participants? If so, what is the nature of these obligations? Second, before embarking on a

clinical trial, should investigators be required to ensure that an adequate supply of the experimental agent exists for all participants in the trial and, if so, for whom and for how long? Should supply be sufficient for participants randomly assigned to the experimental arm to complete the protocol-required courses or for participants randomly assigned to both arms of a trial to allow for the possibility of future crossover? Third, if researchers do owe something to their research participants, how does the extremely limited supply of an experimental agent affect this obligation? Are there other factors that would affect such obligations? For example, does the dismal prognosis of high-risk neuroblastoma change the obligation to study control-arm participants despite the lack of data suggesting a role for Ch14.18 when administered beyond 110 days after SCT? How do researchers reconcile potential obligations to current control-arm participants (using a drug with unproven efficacy in patients beyond 110 days) with the likelihood that use for this group may decrease availability of an active agent for future patients (in whom the agent has proven efficacy)?

THE NATURE AND LIMITS OF RESEARCHERS' OBLIGATIONS TO RESEARCH PARTICIPANTS

“The childhood cancer experience is a relational process.”¹²

Do Investigators Have Reciprocity-Based Obligations?

Before determining if researchers have obligations to research participants, it is important to recall that the purpose of research is to secure generalizable knowledge to help future patients.¹³ Benefiting current research participants is secondary to this goal; unlike physicians who are bound to do what is in their patients' best interest, researchers are tasked with minimizing study risks while protecting participants from avoidable harm.¹⁴ Nevertheless, researchers do have robust obligations toward study participants, particularly when, as in most pediatric oncology research, the investigators serve simultaneously as participants' physicians. When the research in question involves a therapeutic clinical trial, researchers' obligations take on added significance, because research participants also entrust aspects of their health to investigators.

In deciding to join a study, research participants, either voluntarily or on the basis of proxy permission, assume certain risks for the benefit of others. Accordingly, it seems reasonable to recognize their contribution. The decision to participate in medical research is partially determined by the trust of potential participants in the research endeavor in general as well as by trust in the particular investigators.^{12,15-18} This is especially true when participants' health may be affected by participating in clinical research, as in the ANBL0032 trial. In a study of Canadian children with cancer, the most important factor influencing parents' satisfaction with childhood cancer research was the degree of trust in their child's health care team.¹² Patients (and their surrogates) often lack the requisite knowledge or expertise necessary to decide what medical decision or course is best and must therefore rely on belief and trust that physicians, including physician-investigators, will help them decide wisely. Physician-investigators are in a position of potential conflict as they strive to balance the distinct goals of clinical care and research—the obligation to promote what is in the best interest of individual patients versus the obligation to protect the integrity of a research study for the sake of

future patients.¹⁹ Nevertheless, patients and parents considering participation in a clinical trial must be able to trust that physician-investigators will take their interests seriously in important decisions that affect their care.

The nature and basis of researchers' obligations to clinical trial participants are complex. Sofaer et al²⁰ suggest that moral reasons to recognize the contributions of research participants are primarily justice and relational based. Miller and Weijer¹⁸ contend that the investigator-participant relationship places fiduciary responsibilities on researchers, largely based on researchers' ability to influence the interests of participants. Richardson and Belsky²¹ suggest that researchers have moral obligations to participants based on the duties of compassion (awareness of the participants' needs and values), engagement (attention to the individual as a whole), and gratitude (acknowledgment of participants' willingness to assume risks for others).

Moreover, the extent of a researcher's obligations to a research participant is said to be at least partially influenced by the strength of the researcher-participant relationship and the nature of the trial.²¹ Imagine two studies—the first limited to a single encounter between the researcher and participant and involving a relatively minor intervention such as a blood draw, the second investigating a novel therapy for a child with cancer that occurs over several years and entails numerous interactions between researcher and participant. The latter study places a more rigorous set of obligations on the researcher than does the former, particularly as she or he simultaneously has clinical care responsibilities. Similarly, when the clinical condition is particularly severe, when a research participant volunteers for especially risky or burdensome studies, or when the participant is largely dependent on the researcher for care, the researcher's obligation correspondingly increases.

Each of these positions draws from the US National Bioethics Advisory Commission, which has articulated the principle of justice as reciprocity.²² Justice as reciprocity recognizes that were it not for research participants' assumption of risks, investigators would not be able to perform valid experiments or make substantive observations for the benefit of others. Justice as reciprocity demands that researchers recognize and appreciate participants' contributions to the research enterprise as inherently valuable.

An additional argument for researchers' obligations is relational. Sofaer et al²³ found that many research participants, especially those participating in lengthy trials and those with chronic diseases, came to regard clinician researchers as caregivers. The authors argued that these perceptions were not based on therapeutic misconceptions. Rather, participants appreciated the nuances of the researchers' role but nonetheless believed that the researcher-participant relationship established an obligation for researchers to deliver care.

Having established that researchers have *prima facie* obligations to research participants, it is important to consider some factors that may limit these obligations. Two examples of factors that may limit researchers' obligations, which are relevant to all studies, are scientific considerations (obtaining valid answers to study questions) and acknowledging nonstudy participants who might be affected by actions taken within a study. Regulatory constraints may also limit researchers' obligations. Lengthy approval processes for new drugs by agencies such as the US Food and Drug Administration may prevent a researcher from administering a particular therapy. Alternatively, safety concerns and sound clinical trial research design may stand in researchers' way. For instance, phase I clinical trials designed to deter-

mine maximum-tolerated dose enroll only a small number of participants and restrict researchers from offering the drug to more participants. Similarly, as appreciated by the current shortage of chemotherapeutics (and other drugs), researchers may be unable to secure necessary and effective drugs because of scarce supply, quality-control issues, excessive cost, or manufacturing problems.^{24,25} Although the supply of a drug for a specific clinical trial may come up against unanticipated barriers, the study design should in general ensure adequate access to quantities of the drug to complete the scientific objectives of the study. Failure to do so exposes the participants to risk without any prospect of generalizable scientific knowledge. In the present case, the need to assure an ongoing supply of Ch14.18 for children with neuroblastoma prompted the NCI to support COG with the drug supply to keep the ANBL0032 trial open until an industry sponsor could assume production.

Should Investigators Be Required to Ensure That an Adequate Supply of Experimental Agent Exists for All Trial Participants (Including Control Arm)?

As discussed previously, reasons to ensure post-trial access include reciprocating the contributions of research participants and their assumption of risks. In addition, researchers have a moral responsibility to seek to avoid the harm of discontinuing a beneficial intervention. Although individual researchers and research organizations cannot compel drug manufacturers to produce a particular drug, no matter how effective it may be, prior agreements are an important mechanism that can facilitate post-trial access for beneficial interventions.^{15,22,26-28} Prior agreements account for the interests of various stakeholders who are involved in a trial, including but not limited to research participants, investigators, and sponsors. The primary goal of a prior agreement is to delineate, before a trial is initiated, specific measures for providing ongoing access to a proven and effective intervention once a trial ends. This is particularly true for the interval period between the completion of a trial and commercial availability of the agent found to be effective. Agreements to ensure post-trial access may be of particular relevance for control-arm participants who did not receive the active intervention during the course of the trial.

The World Medical Association (WMA) has articulated support for prior agreements to help ensure appropriate post-trial access.²⁸ In considering post-trial obligations, the WMA distinguishes research participants from nonparticipants. Specifically, the WMA restricts obligations of post-trial access to study participants. In the case of ANBL0032, COG and its neuroblastoma committee adopted this approach when deciding to limit the offer of Ch14.18 to the 52 children who had been randomly assigned to the standard-therapy arm and who remained progression free more than 110 days from the time of SCT rather than to all patients with neuroblastoma. Although the COG Neuroblastoma Committee was concerned that the decision to restrict access to an apparently effective but scarce agent may have been perceived as ethically problematic, its decision was consistent with international research guidance.

Many research organizations, including COG, distinguish funding research from funding health care. Although it is unreasonable to expect an organization such as COG to finance costly therapies²⁹ that are found to be effective in trials, financial constraints do not entirely absolve researchers of their commitment to research participants. The approach adopted by the UK Wellcome Trust, a national organization

that funds global research, is instructive. The trust encourages grantees to contemplate, from the beginning, how ongoing access to beneficial findings of research will be supported once a trial is complete.¹⁵ Similarly, the US National Bioethics Advisory Commission recommends that discussions regarding post-trial access occur during the planning phase of a trial and, if post-trial access is not possible, serious consideration be given to whether initiating the trial is appropriate.²² Grady²⁶ argues that at least in the immediate period after completion of a trial, investigators and sponsors are obligated to provide ongoing care. Indeed, she uses precisely the specific example of providing ongoing post-trial access of an effective intervention to research participants while awaiting licensure of the therapy. This is what COG has done while awaiting an industry sponsor to assume responsibility for manufacturing Ch14.18.

How Does the Extremely Limited Supply of an Experimental Agent Affect Obligations to Control-Arm Participants?

As reviewed elsewhere, the hope for a cure, combined with parents' and physicians' willingness to consider all reasonable means to prolong the lives of children with cancer, is an integral component of the childhood cancer experience.³⁰ With this in mind, and against the backdrop of articulate patient advocacy groups calling for expanded access to investigational agents for children with cancer,³¹ it is not difficult to appreciate the position the COG Neuroblastoma Committee found itself in when it decided to offer Ch14.18 only to participants in an ongoing research study rather than on a compassionate-use basis to all children with high-risk neuroblastoma. Thus, the COG Neuroblastoma Committee proactively invited the COG Patient Advocacy Committee to participate in the Neuroblastoma Committee meetings and obtained its understanding and support before reaching this difficult decision. Subsequently, the study chair presented to parents and families a detailed discussion of the beneficial outcome, toxicities, and supply issues surrounding Ch14.18 at a separate meeting organized by the Children's Neuroblastoma Cancer Foundation. These strategies illustrated a transparent process for determining the policy for access to the limited supply of Ch14.18.

Given the limited supply, the dilemma of the COG Neuroblastoma Committee amounted to a choice between offering Ch14.18 to control-arm participants for whom it may or may not be less effective beyond day 110 after SCT and offering it to future participants within the established 110-day window. If many parents of control-arm participants opted to accept Ch14.18, there was a risk that it might be unavailable for some future study participants. Scientific considerations were also relevant; if many control-arm participants opted to cross over, the ability to detect differences in OS, an important secondary end point, as well as the ability of the study to detect differences in long-term EFS would have been diminished, thereby weakening the scientific validity of the intention-to-treat comparison.

It is important to note, however, that honoring research participants' (and their parents') contribution may take a different form altogether and need not solely center on receiving the proven therapy. As recognized by Lavery,¹⁵ in some instances, research participants may no longer be eligible for trial benefits, because they may have "passed the critical window of opportunity for any further benefit from drug administration." Although this situation may preclude researchers from administering the experimental intervention, it does not negate their obligation in full but rather modifies it.

In light of the ethical considerations and the documented benefit of Ch14.18, COG believed that its first obligation was to ensure the ability to treat current and future participants in ANBL0032 who had yet to receive the antibody. This commitment informed the joint COG/NCI decision to keep the study active while taking steps to guarantee a sufficient supply of Ch14.18 for current and future participants.

After carefully considering the cumulative risks and benefits (both to the individual child and to the population of children with neuroblastoma as a whole), the COG Neuroblastoma Committee decided that the offer of Ch14.18 to control-arm participants was ethically appropriate. Arguably, relational factors such as participant and parent trust in researchers, researchers' care responsibilities, and the strength of the participant-researcher bond ultimately persuaded the committee members of the ethical validity of this decision. The complex issues of a lack of evidence regarding the efficacy of Ch14.18 when administered beyond 110 days after SCT and the potential serious adverse effects such as allergic reactions were brought up in the general session of the COG meeting, the COG Neuroblastoma Committee meeting, and the study chair's lecture to the 2009 annual neuroblastoma parent group meeting. COG physician-investigators discussed the trial data and their implications with families of children with neuroblastoma enrolled onto the study. Finally, the COG chair and the COG Neuroblastoma Committee sent an official letter to all participating patients and their families communicating the trial results and expressing gratitude for their participation (Appendix, online only). In the letter, which included the input of the COG Patient Advocacy Committee, parents were encouraged to discuss the implications of the trial with their primary oncologist.

POSTSCRIPT

Although the parents of all eligible 52 children enrolled in the control arm of ANBL0032 were offered access to Ch14.18 after protocol modification, only four parents accepted the offer. Each of these four

Table 1. Framework of Questions to Be Addressed for Control-Arm Participants After Revelation of Benefits of Experimental Therapy

Ethical Issue	Considerations
Researchers' reciprocity-based obligations	Obligation to: <ul style="list-style-type: none"> • Participants actively enrolled onto trial • Past participants Strength of obligation varies according to: <ul style="list-style-type: none"> • Concurrent clinical care responsibilities • Severity of illness • Availability of effective therapies outside the research
Post-trial access	Decide in advance: <ul style="list-style-type: none"> • Which group of research participants will be offered access • How long this obligation persists • By what mechanism the supply of drug will be assured
Balancing scientific knowledge with participant/proxy hope	Consider if beneficial interventions will be offered to participants who do not meet previous eligibility criteria Include stakeholders in decision making

children had completed standard treatment within the preceding 4 to 9.6 months and enrolled at 391 to 550 days after stem-cell infusion. Without directly questioning parents, we can only speculate as to why many parents chose not to receive Ch14.18. In a study examining parental decision making for children with cancer, Hinds et al³² found that a recurring parental concern was the child's quality of life and the associated toxicities of treatments. Many parents also considered choosing good science extremely important. In other words, these parents sought to balance a treatment's promise for a positive outcome with its potential negative adverse effects. One might surmise that the parents of the 52 children in ANBL0032 who remained progression free, and who were therefore offered access to Ch14.18 after the COG Data Safety Monitoring Committee terminated random assignment, relied on similar reasoning. The absence of good science suggesting a role for Ch14.18 when used late after SCT, along with the likelihood of substantial adverse effects, may have informed parents' decision to decline. Alternatively, investigators' discussions about the options may have favored declining antibody treatment. Finally, parents of children who remained progression free may have been unenthusiastic about new interventions that carried substantial burdens for the child. By the time of eligibility for the antibody therapy, most children would have experienced 8 to 10 months of intensive, hospital-based chemotherapy, major surgery, stem-cell harvest and autologous transplantation, and radiotherapy. If not presented as part of the initial expectation of care, the additional 5 months or more of antibody therapy may have been overwhelming.

DISCUSSION

The ANBL0032 trial highlighted several important ethical issues, including the limits of researchers' reciprocity-based obligations to study participants, post-trial access to beneficial therapies and mechanisms for providing ongoing access, and the difficulty of balancing scientific knowledge and participant/proxy hope in the face of a life-threatening disease. Fostering participants' trust in the research enterprise and in individual researchers is integrally linked with investigators' obligations to research participants. When research substantially affects participants' welfare, the obligations of researchers

increase. At the same time, practical constraints such as limited resources, scientific imperatives, and regulatory concerns necessarily limit these obligations. One way to confront these barriers is through deliberative pretrial discussions and planning with relevant stakeholders, highlighting appropriate post-trial obligations and access. The difficult choices confronted in the ANBL0032 trial will likely arise in future clinical trials, highlighting the need for a suitable framework to assist investigators and research participants in balancing these challenging issues. Thoughtful consultation with a multidisciplinary team as occurred in the ANBL0032 trial resulted in a transparent and ethically defensible strategy. This approach provides an instructive framework for how similar challenges can be anticipated and met in the future (Table 1). Responsible and ethical research conduct demands an awareness of these vitally important issues.

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