Is a New Protocol for Acute Lymphoblastic Leukemia Research or Standard Therapy?

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abstract

In the United States, doctors generally develop new cancer chemotherapy for children by testing innovative chemotherapy protocols against existing protocols in prospective randomized trials. In the Netherlands, children with leukemia are treated by protocols that are agreed upon by the Dutch Childhood Oncology Group. Periodically, the Dutch Childhood Oncology Group revises its protocols. Sometimes, these revisions are categorized as research, sometimes as treatment. In this Ethics Rounds, we analyze whether enrollment in a new protocol ought to be considered research and, if so, we discuss the implications of that designation. Our discussion highlights the different ways different countries approach complex issues of research ethics.

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Drs Dekking and van der Graaf, de Vries, and Bierings had the original idea for this article, helped conceptualize the article, and contributed to the manuscript; Dr van Delden and Kodish helped conceptualize the project and contributed to the manuscript; Dr Lantos helped develop the original idea for this article, helped conceptualize the article, and contributed to the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-2327

DOI: 10.1542/peds.2014-2327

Accepted for publication Dec 16, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Drs Dekking, van der Graaf, and van Delden were supported by grant 113203201 from the Netherlands Organization for Health Research and Development. Dr Lantos' work on this project was supported by a CTSA grant from NCATS # UL1TR000001 (formerly #UL1RR033179).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

This Ethics Rounds analyzes a case that illustrates the intertwinement of research and care in the evolution of pediatric oncology. To analyze the case, it is necessary to understand how pediatric oncology innovation is organized in the Netherlands. There, the treatment of acute lymphoblastic leukemia (ALL) in children is developed in a way that is somewhat different from that in the United States. The Dutch approach raises some interesting questions of research ethics.

In Dutch pediatric oncology, patients with ALL are treated by a nationally agreed-upon protocol. Periodically, pediatric oncologists meet to review their results and results from other countries. Based on this analysis, the protocol may be revised. They then treat all patients with the new protocol and carefully monitor outcomes in comparison with historical controls and with studies done in other countries. In various other European countries pediatric oncologists also adapt their treatments according to

recent insights without necessarily considering them as research.¹

In the United States, most children with cancer are treated on research protocols. These protocols evaluate new approaches to treatment. The new approaches become the standard treatment only if the results of the research show that they are better than existing treatments. In the Netherlands, new or innovative treatment approaches are not necessarily regarded as medical research. Often, innovative treatments are provided without a concurrent, randomly assigned comparison group.

This approach raises a number of questions about the ethics of innovation. Should treatment with a new but professionally endorsed protocol be considered research? If so, should it be reviewed by a research ethics committee (REC)? What sort of consent process is appropriate for this innovative treatment protocol?

With that in mind, we asked experts to analyze a case of innovative treatment

in childhood ALL. Our experts include a group of Dutch oncologists and ethicists who are familiar with the system and an American oncologist and bioethicist whose research analyzes the informed consent process.

THE CASE

In 2004, pediatric oncologists of the Dutch Childhood Oncology Group (DCOG) developed a new protocol for the treatment of children with acute lymphoblastic leukemia (ALL). This DCOG ALL-10 protocol was based on previous DCOG ALL protocols and on the findings of national and international ALL studies. Pediatric oncologists considered the ALL-10 protocol to be the best available treatment. The ALL-10 protocol also contained a significant modification compared with previous ALL protocols. After initial treatment, patients in the ALL-10 protocol were assigned to 1 of 3 different risk groups based on minimal residual disease (MRD) levels. MRD level had been shown to be a strong prognostic factor,² but it had not yet been used in the Netherlands to tailor therapy to patients with different MRD levels. The modification in the ALL-10 protocol was that intensity of treatment was based on whether patients were thought to belong to the standard-risk (SR), medium-risk (MR), or high-risk (HR) group. Patients in the SR group would get less intensive treatment than they would have before using ALL-10. Those in MR and HR groups would get more intensive treatment. Because risk stratification with accompanying tailoring of therapy had not been done in previous protocols, the ALL-10 protocol might have been considered experimental.

As is common in the Netherlands, the results of the ALL-10 protocol would be systematically collected, analyzed, and compared with historical controls. Patients would not be randomly assigned prospectively. Stopping rules were established, and a data and

safety monitoring board would have access to data on side effects and serious adverse events, to assess whether the protocol should still be followed.

Doctors acknowledged that they did not really know the risks and benefits of the treatment regimen of ALL-10. However, based on existing evidence and expert opinion, they strongly believed that it would lead to better outcomes. Because of the small number of patients with ALL in the Netherlands, it was not possible to design a sufficiently powered randomized study. In addition, the pediatric oncologists would not have felt comfortable randomly assigning patients to the new protocol or 1 of the previous protocols.

The pediatric oncologists submitted the ALL-10 protocol to an REC. The REC reviewed the protocol and determined that it could be exempted from research ethics approval because they did not think it constituted medical research with human beings as defined under Dutch law. According to the Dutch Act on Medical Research Involving Human Subjects, patients are participants in medical research if they are "subjected to acts or are required to follow a certain behavioral strategy."³ Both the pediatric oncologists and the REC members regarded the intervention provided by ALL-10 as standard treatment and therefore not as a research intervention to which patients were subjected. Parents and older patients were requested to provide written informed consent for receiving treatment according to ALL-10.

Should this approach to the treatment of ALL be considered research? Should it require approval of an REC? Should parents be asked to consent to research?

DRS DEKKING, VAN DER GRAAF, DE VRIES, BIERINGS, AND VAN DELDEN COMMENT:

To decide whether the ALL-10 protocol needed research ethics

review, we have to determine whether the protocol constituted medical research or standard treatment. The first relevant feature in this respect is that the ALL-10 protocol involved a new treatment regimen. The fact that something is new does not necessarily define its use as research. As stated in the Belmont Report,⁴ although new procedures should not be automatically placed in the category of research, major innovations should be made the object of formal research to determine whether they are safe and effective.

There were reasons to be concerned about the safety and efficacy of ALL-10. The risk stratification and corresponding intensification of treatment of patients in the MR and HR groups may have led to unforeseen risks and expected benefits. Moreover, the aim of the ALL-10 protocol was to evaluate the innovative treatment regimen in terms of overall survival rates and to see whether they were indeed higher than previously. From this evaluation, the pediatric oncologists wanted to obtain knowledge that would be generalizable to the group of patients with ALL and would help in providing directions for future therapy. The uncertainties surrounding the level of risk of the new elements of the ALL-10 protocol suggest that it would have been appropriate to consider the protocol experimental, and thus it would have been appropriate to formally and fully study the outcomes.

One way to prevent unreasonably high-risk research activities and to protect patients is to submit research protocols to an independent REC. If the ALL-10 protocol ought to have been considered research, then it should have been submitted to an REC as a research protocol.

However, the goals of the oncologists were primarily to do what was best for their patients. In their collective clinical judgment, the ALL-10

protocol, as designed, was the best treatment available for all patients with ALL. Therefore, they thought it was appropriate to present the ALL-10 protocol as standard treatment and, at the same time, to monitor the safety and efficacy of this protocol as a way of checking to see whether their collective clinical judgment was correct. This method was in line with the follow-up of all patients according to DCOG standards, which is done for all protocols including observational protocols. Also, in addition to a lack of sufficient power to design a randomized study, they did not think it was ethically appropriate to randomly assign patients because doing so would mean that half of the patients would not receive what the pediatric oncologists considered best available treatment, that is, treatment according to ALL-10.

As discussed by Kass et al,⁵ research and treatment are not so easily distinguishable if “the production of knowledge [is] an essential part of the routine practice of medicine.” These authors refer to pediatric oncology as an example of a situation in which the routine practice of medicine can also produce new and generalizable knowledge. In such situations, a health care system becomes a learning health care system, that is, a system “in which knowledge generation is so embedded into the core of the practice of medicine that it is a natural outgrowth and product of the healthcare delivery process and leads to continual improvement in care.”⁶

The idea that research can be an essential part of medical practice is relevant for our discussion, because the ALL-10 treatment protocol integrated aspects of research and aspects of treatment. It was designed to simultaneously develop generalizable health knowledge for the group of patients with ALL and to optimally treat current individual patients. Thus, the ALL-10 treatment

protocol seemed to be a well-balanced hybrid between research and care. Patients treated according to ALL-10 would receive what the pediatric oncology community considered to be the best available treatment while this treatment was simultaneously evaluated for efficacy. Consequently, it is difficult to categorize this kind of protocol. However, this difficulty does not mean that such protocols should necessarily be considered treatment protocols. In this case, the uncertain level of risks associated with the innovative elements of the treatment regimen leads us to conclude that the ALL-10 protocol should have been considered a research protocol, with appropriate research ethics review according to the Dutch Act on Medical Research Involving Human Subjects.

We should note that adopting the ALL-10 protocol as a research protocol would not have changed the options available to patients, because for the pediatric oncologists it would be unthinkable to also offer an older protocol. They commonly believed it unethical to withhold a treatment from patients when the whole Dutch pediatric oncology community regarded ALL-10 as the best available treatment. As soon as a new protocol has been developed, the previous protocol is considered outdated. Therefore, for the pediatric oncologists offering a previous protocol did not amount to a meaningful choice. Rather, it would have meant delivering suboptimal care to give patients and parents freedom of choice. Therefore, we think that the proper approach to consent should have been to inform patients and parents that ALL-10 was an innovative treatment, albeit one that is recommended by all Dutch oncologists.

This case illustrates a situation in which a treatment does not fall neatly into 1 of the 2 categories of research or conventional treatment. It remains to be discussed how to review hybrid

protocols that integrate a research goal with the objective of simultaneously providing individual patients with best current treatment. In line with Kass and colleagues,⁵ we think that a change in both research ethics regulation and oversight of conventional care is needed. We should strive for a research oversight system that is able to do at least 2 things. First, it should accommodate hybrid protocols and other practices that integrate research with care. This system may call for a different review method and may have implications for the informed consent process when research and care cannot be separated. Second, interventions that are considered standard care should be ethically reviewed because of the absence of available data on safety and effectiveness.

DR KODISH COMMENTS:

“Research is the standard of care for children with cancer.” This was the battle cry in the late 1980s and early 1990s, when I was training to become a pediatric oncologist. Because I was also doing a fellowship in medical ethics it left me deeply confused. How could something that is experimental be considered the standard of care? How could we allow children who were newly diagnosed with ALL to be treated off-study if we knew that being in a clinical trial was best for them? And finally, how could we be serious about a choice associated with informed consent when our mentors considered it a failure for parents or older children to refuse study participation?

Now, in 2015, the strict dichotomy between research and clinical care that was a seemingly foundational commitment of bioethics in the late 20th century appears to be fading, and concepts such as the learning health care system cause us to refocus on the inadequate evidence base for treating children who are *not* enrolled in clinical trials.

Let us look at the modification. For the first modification in protocol ALL-10 compared with previous protocols (assuming that the data are persuasive), risk stratification is ethically justified by the fact that efficacy and toxicity are both important considerations in the care of children with ALL. Despite the advent of molecular oncology and targeted therapy, there remains a tight link between dose, efficacy, and toxicity. It is therefore axiomatic that children should be exposed to the lowest possible dose of chemotherapy necessary to achieve cure. Giving too much will lead to unnecessary acute and long-term side effects, and giving too little will risk death from disease.

What about randomization? Doctors acknowledged they did not “really know” the risks and benefits of the new treatment regimen. How do we “really know” anything? I recently saw a bumper sticker that said, “The good thing about science is that it is true whether you believe it or not.” Paul Simon says, “Faith is an island in the setting sun, but proof is the bottom line for everyone.” The strong belief of the Dutch pediatric oncologists that protocol ALL-10 would lead to better outcomes seems to be another example of faith-based medicine, albeit based on expert opinion and results from other studies. I argue that they have an ethical obligation to reconsider and that equipoise has not been disturbed. Despite the low incidence of treatment-related mortality, secular trends in supportive care may account for improvement in outcomes for protocol ALL-10 over protocol ALL-9 or protocol ALL-8, and the question of which regimen is better may never be answered without a randomized controlled trial. If ALL-10 is better than previous protocols, which modification is having the impact? I advocate for evidence-based care of children with cancer and suggest that a randomized controlled trial would be ethically preferable and

statistically more rigorous, at least for patients in the MR and HR groups. Having said that, I think the decision made by the Dutch pediatric oncology community and the REC is not unethical by any means. Because stopping rules had been established, the data and safety monitoring board was able to look carefully for evidence of inferior outcomes (both efficacy and toxicity). If that were to transpire, shifting back to protocol ALL-9 or ALL-8 would be ethically obligatory.

In conclusion, this approach to the treatment of ALL should be considered research but should not, in my opinion, require the approval of an REC. This may be somewhat radical, but why not uncouple the definition of research from the requirement of review? The current definition of *research* that triggers the need for regulatory review hinges on whether the project will contribute to generalizable knowledge. This threshold is too low. In this case, with an eye toward the learning health care system, I would reinterpret the definition and trigger based on considerations I presented earlier. The comparison with historical control holds the promise of developing generalizable knowledge but does not, in my mind, require additional regulatory review. Proposals that have no prospect of direct benefit to children and are above minimal risk should still be reviewed, as should projects that expose children to high risk without concomitant benefit. Additionally, randomization might be considered an automatic trigger for regulatory review (although some may reasonably disagree with this suggestion). This way, current and future children will benefit from research without added regulatory burden on the investigators, institution, and REC. In contrast, if a decision were made in this case to conduct a randomized trial (as I would suggest as ethically and statistically preferable), review by the REC would in my view be necessary.

We need more evidence-based medicine and should push to truly become a learning health care system. In many ways, pediatric oncology has been the poster child for the learning health care movement. Having worked as a clinician and researcher in this context for many years, I am confident that nearly all parents and older children with cancer are eager to help other children and families facing the same disease and would gladly remove barriers to progress. If studies are designed to avoid the addition of any incremental risk and are closely monitored for adverse events, they can be safer than cancer care outside the clinical trial realm. Meaningful informed consent should focus on risks, benefits, and alternatives, not false dichotomies between research and standard care.

DR LANTOS COMMENTS

Prospective randomized clinical trials in children should be done only when doctors are genuinely uncertain whether one treatment protocol is better than another. If doctors believe that one approach is better, it would be unethical for them to randomly assign children to the approach that they thought to be inferior. Each doctor must decide just how certain he or she is that one treatment is better. This decision should include consideration of the basis for that certainty. Is it based on personal experience, consultation with colleagues, professional society statements, or evidence from clinical trials? Each might allow different degrees of certainty.

Tension arises, however, because any judgment about whether an innovative protocol is better than an existing protocol must rely on historical data. In this particular case, there were data on the older protocols from their widespread use in the Netherlands. There were data on the new protocol from its use in different clinical populations. Such data must form the basis for any

conclusions about the relative safety and efficacy of the older protocol and the proposed newer one. If a careful review of the historical data leads doctors to conclude that they are uncertain as to which is preferable, then they ought to do a prospective randomized trial. However, if the data allow a conclusion that the 2 approaches seem similar, they can also allow a conclusion that 1 appears to be superior. If the approach that appears to be superior is the older one, then there would be no reason to try the newer one. However, if the data suggest that the newer approach seems better, then it is unclear whether a prospective trial is the best way forward or whether, instead, the approach of simply adopting the newer one is ethically preferable. The tension, then, is in the ways we come to conclusions about relative safety and efficacy.

As information systems gets better and computing capacity increases, we should be better able to make judgments based on careful analysis of retrospective data. The Dutch approach seems to be a reasonable way to balance the risks of innovation and the desire to ensure that all patients get the best possible treatment.

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