Part 1: Hope Against Odds

Ethical issues pertaining to patients and clinical trial subjects facing life-threatening diseases

By Linda Strause, Ph.D.

Life can change in an instant, but something always abides—hope. When faced with a life-threatening disease, hope—the unfailing feeling and expectation that tomorrow will be better—challenges autonomous decision making and explains why only 3 to 5% of cancer patients participate in clinical trials. Although oncology trials account for almost 31% of clinical trials globally[1] they remain the most difficult therapeutic area to investigate. As an industry, clinical professionals must learn to put the patient at the center of the clinical trial enterprise and see this approach through their eyes.

My personal story

Hope seems like a simple concept, but managing hope isn't. Managing hope became a challenge as I began my journey one spring when a neurosurgeon said, "Your husband has glioblastoma multiforme (GBM), an extremely aggressive, highly vascularized and incurable brain cancer."

I learned, from a personal and professional perspective, that although hope remains a constant, it changes form. When our neurosurgeon said, "Someone is on the right side of the curve," it made perfect sense to me as a clinical research professional. In the beginning, we hoped for a cure. As time and the disease progressed, our hope changed.

You must find a balance between your hope that the standard of care (SOC) will work, that the investigational agent in a clinical trial will work and that there will be dignity in death. How hope changes depends on the alternatives available to the patient at any given time.

A new reality

Plans for a dinner party snagged when 58-year-old Randy, my husband of 35 years, remarked that he just "didn't seem right" with noticeable concern in his voice. I called the doctor, who advised a trip to the emergency room. Everything seemed so normal until I took him into the emergency department. The next thing I knew, someone was asking my husband to count backwards by 10 and he couldn't do it.[2] That was when we embarked on our new reality.

A glioblastoma tumor is like an octopus. It's difficult to surgically remove all the tendrils without jeopardizing the brain. Consequently, even when the primary tumor is removed, microscopic ones remain. Doctors recommended a three-phase treatment plan. A balloon implanted during surgery was injected with radioactive iodine and removed after six days. Randy received local radiation five days a week and low-dose chemotherapy daily for five weeks. In mid-summer, he received high-dose chemotherapy five times over the course of a month.

Even with a plan in place, I began exploring options. It's hard to imagine anyone better suited to navigate the clinical trial process than I was. I have a doctorate in neurophysiology and I am the executive director and head of clinical operations at a biotechnology company where I have conducted oncology research for years and currently manage a phase 3 melanoma trial. Suddenly, I was completely responsible for Randy's care, and for making life and death decisions.

For the first time, I experienced how difficult it is for patients to navigate their way through the clinical trial process. As much as I liked, respected and trusted our medical oncologist, he was primarily familiar with the trials at the academic cancer center where he practiced. My professional experience with www.clinicaltrials.gov led me to strongly believe this website was more suited to researchers' and sponsors' needs more than would-be participants'. As I reached out to colleagues and friends for opinions and recommendations, I could not help but wonder how people without access to such a network coped.

As chair of a hospice research ethics committee for 15 years, I understood the concept of morality, the protection of human subjects and the ethical principles that guide clinical research. Therefore, I

understood why our oncologist would not try to influence me when I explored potential clinical trial participation. He would not (and should not) say, "I think this is the best choice."

Navigating care paths

Avoiding the therapeutic misconception is something that we train our investigators to do. To protect human subjects participating in clinical research, one must avoid coercion to maintain the individual's autonomy. However, the reality is that as ethical and proper neutrality may be, it puts an enormous burden on the patient and the family who are desperately trying to discern the best care path. No one is there to help you navigate between SOC and research choices. In the end, you make the best decisions you--and you alone—can make, because there is no one else to make the decision for you.[2]

Hope as a deterrent

Hope may be one of the greatest obstacles to clinical research participation. For cancer patients, scans become a part of life. Periodically, you have a good scan that would provide a little glimmer of hope. Randy went to work every day, void of symptoms, and life seemed somewhat normal. I would think to myself, "This is working. There is hope." Because of hope, patients and their families often choose the path of SOC because it is known and understood by their physicians and healthcare providers. I understand why so few cancer patients participate in clinical trials—it is because of hope.

However, I knew the odds were against him. SOC treatments work for only about 2% of patients. Still, given my research experience, I knew the odds of success with a phase 1 or 2 trial were even lower or, at best, unknown.

The management of hope requires the consideration of the success rate for SOC, which is predicated on the data submitted for approval, and the proposed success rate for a clinical trial based on scientific assumptions. If 2% of patients respond to an approved treatment and 10% responded to an investigational agent, which one would you choose? These statistics may be meaningful to physicians and researchers, but they are often meaningless to the patient and family. From my seat on the other side of the table, I wasn't interested in generalizable results. I wanted to keep Randy alive so I held on to

the hope that the outcome with SOC would be favorable, that he would be on the "right side of the curve."

When do you reach the point of deciding to participate in a clinical trial? For many patients and families facing life-threatening diseases, you wait until it is clear that traditional SOC treatments are no longer working. Yet, by the time it was clear that the SOC was not working for Randy, he no longer qualified for the phase 2 clinical trial we considered. He didn't meet the trial's requirements because he received too many treatments.

With no other choices available, our hope changed. Our two sons moved home, the hospice was called in and we held on to the hope that there would be continued quality of life and dignity in death.

Just before midnight on April 16, 2010, Randy died at home, surrounded by his family.

Changes for the future

Clinical research professionals must understand the enormity of the decisions they present to would-be participants. Sponsors should be challenged to consider the ethical issues facing patients and families with life-threatening diseases when designing protocols and preparing to recruit research subjects. Innovation in medical care will come from personalized medicine, targeted therapy, gene therapy and new technology.

Although there are many changes the drug development industry could consider, I believe clinical research professionals can and must pragmatically alter their practices to better meet the needs of study volunteers. We must redefine how we look at oncology clinical trials and see these trials from the patient's perspective. This includes understanding the impact of autonomy and obtaining informed consent, developing appropriate clinical trial design, and improving access to clinical trial information while paying special attention to those volunteers facing life-threatening diseases.

In Part II of this series appearing in* Healthcare Update *next month, Strause further examines the role of hope in the treatment of life-threatening diseases and explores clinical trial design.

About the author

Linda Strause, Ph.D., is the executive director and head of clinical operations for Vical in San Diego where she is responsible for the conduct of all aspects of a phase 3 clinical trial in malignant melanoma and infectious diseases. Her passion for end-of-life care began as the director of education and research at the San Diego Hospice, where she also served as chair for more than 15 years. She is the founding chair of the hospice's palliative care and research ethics committee. Strause is also a member of the advisory board for the Journal of Empirical Research on Human Research Ethics*, chair of the regulatory affairs committee and a past board of trustees member for the Association of Clinical Research Professionals, a founding member of the Center for Information and Study on Clinical Research and chair of the Soul Sitters Advisory Board. Combining her work in the conduct of oncology clinical research with the ethical issues pertaining to the protection of human subjects, specifically those facing life-threatening diseases, Strause has been an invited speaker at numerous conferences and is widely published.*

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