COMMENTARY

Research Battles: Survival Tips From a Veteran

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Abstract

Studies of nonorthodox medical treatments may go awry because of inherent flaws in designs that are better suited for trials of pharmaceutical products. Unintended consequences may follow from efforts at randomization, the lack of lead-in periods, required visits for medical assessment, inadequate screening, and a lack of trial publicity. A veteran of a mismanaged trial shares her experiences.

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The commentary in the October/November 2014 issue of *Integrative Medicine: A Clinician's Journal* about the flawed conclusions behind recent negative publicity about niacin reminded me of the challenges faced by those who would study any kind of medical treatment that is outside the mainstream.[1] Because some of the journal's readers may be embarking upon clinical research themselves, as a veteran of such an effort, I thought that an account of our experiences and struggles might help them avoid some pitfalls.

As background, during a 28-year period until his untimely death in July 2015, Dr Nicholas Gonzalez and I have been applying a very intensive nutritional approach to the treatment of advanced cancer. The regimen involves dietary changes; large amounts of nutritional supplements including pancreatic enzymes; and detoxification routines, such as coffee enemas, which patients implement at home after receiving instruction at our office. Dr Gonzalez originally presented a "Best Case Series" of 25 patients with exceptional outcomes at the National Cancer Institute (NCI) in 1993. As a result of that session, the NCI suggested that we proceed with a pilot study that would evaluate our approach in the treatment of inoperable pancreatic cancer. We published the results of the pilot study in the peer-reviewed journal *Nutrition and Cancer* in 1999.[2] On the basis of that study, which documented results far beyond what had previously been reported for the disease, the NCI then agreed to support a controlled trial, comparing our approach to chemotherapy in the treatment of inoperable pancreatic adenocarcinoma. The trial was administered through a major academic medical center in New York City.

Unfortunately, the trial was poorly run and ended in discord, with what we believe to be meaningless data published by the academic researchers involved.[3] Dr Gonzalez's book, *What Went Wrong: The Truth Behind the Clinical Trial of the Enzyme Treatment of Cancer*,[4] goes into detail about the problems with the study, including a number of issues not discussed in this article that I sincerely hope are confined to the institution involved and are not endemic to the medical establishment. In the current article, I will focus on the problems in trial design that, I believe, doomed the project from the beginning.

Design: Randomization Versus Case Control

Randomization is the gold standard for clinical trials, and it was not a problem in a study of our enzyme preparation in a pancreatic cancer model in mice—the mice received either water with pancreatic enzymes or plain water, and the mice whose water contained pancreatic enzymes did much better.[5] But people are not mice, however, and when the treatments being compared are as radically different as those in our study—which compared

chemotherapy to our nutritional approach—people may not agree to randomized participation. Because of poor accrual, the academics running our study finally agreed that the trial needed to be changed to a case control study, so that patients could choose their treatment methods. Nonetheless, years later, our office was receiving calls from patients who were concerned that trial entry might mean that they would be forced to undergo chemotherapy. We believe that accrual continued to suffer throughout the study from that initial misstep.

Lead-in Period

Our pilot study included a lead-in period, during which time patients were supposed to follow the prescribed diet, take their nutritional supplements, and perform coffee enemas. If a patient could not or would not comply with the various aspects of the therapy, they were not entered into the trial. This type of lead-in period is uncommon in chemotherapy trials, because medications are usually administered intravenously and compliance is easy to document.

In studies of a self-administered lifestyle or dietary treatment involving radical change for the patient, such as was required by our nutritional protocol, lead-in periods or elaborate screening processes to assess motivation and the probability of compliance are the rule, not the exception.[6] In the Diabetes Control and Complications Trial, which established that tight control of blood sugar with a strict diet and multiple daily insulin doses can drastically decrease rates of complications of the disease such as blindness or kidney failure, patients went through approximately 40 hours of prescreening before enrollment.[7]

Such extensive screening would not have been possible in our clinical trial, but a lead-in period would have precluded formal entry of the patients who inevitably would not follow through with their treatments. We argued strongly for a lead-in period to be included in the study design, but the chief investigators, who were experienced with research involving drugs but not dietary or lifestyle modification, categorically refused. Without the lead-in period, we ran the risk of having a large number of patients who signed up but then, for whatever reason, would not follow the prescribed nutritional regimen. And that is exactly what happened.

The entry criteria for the study required that patients be able to eat 3 meals per day—a critically important consideration when pursuing a treatment that requires following a diet and swallowing large numbers of capsules. Patients were entered into the trial who claimed that they could eat those meals yet, only days after trial entry, were hospitalized for dehydration and inability to eat. Patients such as these and their families may have been in denial about their difficulties with food intake. However, we believe that some patients deliberately exaggerated their conditions because they were desperate, perceiving entry into the trial as their only hope.

Of the 39 patients who were assigned to receive treatment from us, 16 (41%) were not following their protocols within 1 month of beginning treatment. Two never opened the box in which their supplements were shipped, yet they were considered as fully treated because of the intent-to-treat aspect of the study protocol. A brief lead-in period would have prevented that outcome.

Interference From Outside Practitioners

Patients were required to see a physician monthly for an examination and blood work, as is standard for chemotherapy regimens with their associated toxicities. Almost all of the patients who were entered into the nutritional arm lived far from New York, and, consequently, saw a local physician for those visits—typically an oncologist. We had hoped that oncologists, in the setting of a clinical trial, would be supportive of the patients' choice of treatment. But with only 1 or 2 exceptions, the physicians were quite hostile to our regimen. For example, if a patient were doing well, often the consulting physician would comment on how tragic it was that the patient had chosen to spend the last months of life following a restricted diet. If any kind of problem arose, the physician would aggressively push chemotherapy or try to dissuade the patient from continuing the nutritional protocol.

Imagine trying to quit smoking if every month you were forced to go see a health practitioner who reminded you that the majority of people who try to quit resume smoking again. Imagine trying to lose weight if every month you were reminded that most people cannot lose weight and that even those who do cannot keep it off. The patients in our trial, required to make major lifestyle changes and facing a life-threatening illness, were subjected to this kind of negativity, which, not surprising, affected compliance.

Patient Screening

Since 1987, when we opened our practice, we have had efficient screening mechanisms in place to evaluate a patient's suitability for the treatment we offer. By the terms of the trial, however, we had no input whatsoever in patient selection, because the conventional researchers in charge were convinced that our involvement in screening would introduce bias. We were required to refer all patients who had been diagnosed with pancreatic cancer and called our office to the principal investigator and to treat on trial whatever patients were sent to us.

The screening process was conducted in the office of the principal investigator, a busy surgeon, with presumably many other projects and activities competing for his attention and time. Many patients interested in entering the study for the nutritional treatment contacted our office in desperation, asking us to speed up the process. We suspect that many other patients, pressured by the urgency of their diagnosis, simply gave up and went elsewhere for treatment. Had we been able to manage the screening for our part of the trial, we believe that we could have

recruited a group of participants who were more compliant in following the protocol, while offering all applicants the courtesy of an expeditious review.

Trial Publicity

To accrue adequate numbers of patients into any clinical trial, patients must know that it exists. Any publicity, even a factual discussion of the trial on our own Web site, had to have institutional review board (IRB) approval. The academic researchers believed that asking the IRB to approve Web site text or advertisements would be a fruitless endeavor. We were thus in the peculiar situation of being forbidden to discuss the trial of our work on our own Web site, other than to provide an instruction for interested patients to call the office of the principal investigator. Unsurprising, patients told us that the dearth of information about a government-sponsored clinical trial of our work was odd. I would suggest that investigators make the planning of trial publicity a high priority before actually beginning the study.

Survival Tips

Looking back, I believe that our study would have had a different outcome if (1) we had been able to screen and recruit patients ourselves, with a short lead-in period to weed out those who could not follow the treatment; (2) we had been able to manage the trial ourselves with a referral to an outside physician only when a patient needed it; (3) matched control patients had been recruited from the pool of patients receiving chemotherapy at the academic center involved; and (4) the trial publicity had been planned for and approved from the beginning.

Perhaps such a study could be managed better now, because I do think that the academic medical world is more aware that a nontraditional therapy involving lifestyle modification cannot be stuffed into a box designed to evaluate a pharmaceutical product. However, I would suggest that any researcher evaluate the parameters of their study's design very carefully, with an eye to how they might affect patient compliance.

On a positive, despite all the issues surrounding the study, a patient of mine, who had had a biopsy of an adenocarcinoma of the exocrine pancreas with the pathology subsequently confirmed at the Mayo Clinic and who had been denied entry into the trial because she was technically eligible for surgery that she had refused to have, is now a cancer survivor 14 years later. She has received no treatment other than our nutritional approach as a private patient. She wrote a foreword for Dr Gonzalez's book about the study, *What Went Wrong*.[4] Patients such as her help keep me motivated to continue the work, to see patients with no curative options in standard medicine, and to collect case reports, in the hopes of preserving Dr Gonzalez's legacy of dedication to scientific truth and of keeping a valuable treatment modality alive.

References

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Table 1. Survival Tips

Characteristic of Study	Tip
Randomization vs case control	If the studied interventions are too different, patients may refuse to enroll (eg, a nutritional treatment vs chemotherapy).
Lead-in period	Lifestyle interventions need a lead-in period to improve the chances that enrolled patients will follow the protocol.
Outside practitioners	If the intervention is controversial, outside practitioners may interfere with the patient's compliance with the protocol.
Patients' screening	Prior to the start of the trial, make sure that the investigators will be able to do the screening in an effective and efficient manner.
Trial publicity	Have it planned before starting the trial to ensure that procedures are in place to alert potential participants to the trial's existence.