Clinical Trials in Cancer

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Abstract
Randomized controlled trials (RCTs) in cancer are expensive, slow, and often preclude other exploratory investigations that might be valuable. Two types of RCTs should not be conducted. When the results of exploratory studies are so dramatically different from all prior experience, RCTs should be done to improve upon the new finding but not to allocate some patients to inferior control arms to see enough contemporaneous failures to “prove” the superiority. The other preclusion are RCTs that aim for so small or unimportant a likely benefit that the outcome will not be worth the effort. A study not worth doing is not worth doing well. RCTs in cancer are best used to establish moderate differences, suggested by exploratory trials, that have a real chance of advancing the field. If the entry criteria and end points are sufficiently explicit, e.g., biopsy proof of cancer and death, observer bias will not be a major factor.

The controlled clinical trial is one useful mechanism for examining cancer therapies, particularly when the natural history of the disease may be variable and where the therapeutic effects may be partial, temporary, and difficult to establish unambiguously. Such a trial with a control group receiving the best known treatment, or no treatment if that is ethical, provides an effective comparison.

There is a tendency to assume that the results of randomized controlled trials are so believable that they dominate the standards of clinical practice. Such is not always the case. Not every trial needs to be a randomized controlled trial. Two types of trials should not be conducted in this fashion.

One example of a trial that should not be a randomized controlled trial is when the initial results are so striking and the database of prior experience so uniform that the conclusion is inescapable. The effect of methotrexate on choriocarcinoma (1), the effect of vincristine and prednisone on acute lymphocytic leukemia of childhood (2), the effect of the nitrogen mustard/vincristine/procarbazine/prednisone (also known as MOPP) regimen on Hodgkin’s disease (3), the effect of cisplatin, vinblastine, and bleomycin on testicular cancer (4), and the effect of Adriamycin plus methotrexate in the adjuvant treatment of osteosarcoma (5) are examples of logical, intuitive, or lucky observations that were so stark a difference from contemporary experiential expectation that they were accepted by knowledgeable observers as a new truth revealed. These observations constituted some of the giant steps in cancer medicine. Fine tuning of these regimens after the crucial initial observations required more cases and contenting oneself with incremental advances after the quantum leap. As a technique of establishing the validity of the pioneering observation, however, randomization to no treatment has in some instances been pursued with the fervor of religious zealotry for the controlled clinical trial (6). When morbidity and mortality in the untreated group was tallied, some considered it a justifiable cost of investigation. That, I believe, is a misuse of biostatistics. Indeed, prescient biostatisticians on occasion have adopted the “play the winner rule” for just such a situation. So long as the treatment is successful, the next patient continues to receive it. If one encounters a failure, the following patient receives the opposite treatment. This technique would certainly limit the exposure to an inferior treatment but is not easily applicable for situations where the results are delayed. Knowledge of the disease, its history, and therapeutic expectations would avoid even this, however. Energy could better be placed in studying improvements rather than slavish adherence to random allocation to a palpably inferior control.

Random allocation is highly appropriate where background noise and subjective interpretation could easily mislead. Where the observation represents a sea change, based on unmistakable objectivity, such as curing a high proportion of previously incurable patients with cancer, the wisdom and experience of the observer reach the goal sooner, and with a shorter casualty list. A professor of biomathematical sciences counseled me once that if he looked out the window and saw a man walking two feet above the ground, with nothing between his feet and the grass, he would not even need a series of two.

In clinical investigation, randomization is a complex social interaction between physician and patient that implies the physician has no reason to believe one treatment is superior to another. This is sometimes not the case. Glidewell and I suggested a study of this phenomenon (7). Doctors who use a treatment because they believe in it, are familiar with it, and apply it effectively may indeed get better results than those who approach the method gingerly and with reluctance because they are unfamiliar with it or disbelieve it will prove effective. We suggested that in a large cooperative group, three large subsets of patients could be assigned contemporaneously. The first class would be patients treated by physicians who chose the regimen that they thought would be most effective. Some physicians would choose A and some would choose B (doctors by choice). The second class of patients would be treated by physicians who could not conscientiously state they favored one or the other regimen and thus were willing to be randomized so that all their patients would be treated by regimen A or by regimen B (doctors at random). The third class of patients would be those

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whose physicians participated in randomization as is conventionally done (patients at random). We postulated that the comparison of the outcome of these three groups of patients might provide valuable data. It might serve to quantify the impact of background noise, bias, and other assumed pitfalls of unrandomized studies. It certainly would increase the number of patients who enter clinical trials, because there are both physicians and patients sufficiently uncomfortable with randomization of the patient that permission is denied. A patient who heard that the physician was using treatment A because he or she believed it to be the better of the two (doctors by choice) would likely feel greater security. A patient who was offered treatment B by the physician who said there probably was no difference between the treatments and therefore he or she was using B (or A; doctors at random) might also have the confidence that his or her physician had already crossed the perilous decision point. Patients randomly allocated in the conventional way might sustain the conventional apprehensions and anxieties about the procedure; and as is often the case, they might wonder if they might have done better on the other arm. A psycho-oncological study of patients in the three classes at the time of allocation would be of interest. A study of the outcome might, I believe, show that entirely valid results could be obtained by qualified individuals using objective criteria in matched sequential series. If such were the case, it would avoid the subterfuges that have sometimes tainted the purity of the randomized clinical trial, such as "pre-randomization" (so that the patient would not be confronted with a choice), and the fiction that there is absence of investigator bias when a dramatic advance has been associated with a new treatment regimen and the control arm is the usual hum-drum.

To be certain, few of the hundreds and thousands of trials conducted in cancer have had the dramatic departure from expectations described in the first exception above.

The second type of unnecessary randomized controlled clinical trials in metastatic cancer is the study of procedures or phenomena of such little promise that the effort is disproportionate to the expected outcome, substantially more costly, and slower. If a study is not worth doing, it is not worth doing well. Turning loose the creative energies and imaginations of talented investigators who were seeking dramatic advances way out in deep space might reap a richer harvest in new approaches to cancer than fielding a platoon of more conservative players who were content to bunt rather than swing for a home run.

Thus, the controlled trial should be worth the effort and reserved for important questions where preliminary evidence suggests a modest improvement. A truly major improvement where there has been little of previous value does not need a randomized trial for its proof. To set out to prove a minor advantage requires a very large controlled trial and probably usurps too many resources in the form of intellect, patient material, money, and the emotional energy that is sometimes the indispensable driving force for investigation.

I have suggested that carcinomas and sarcomas, often blithely called solid tumors, could be better conceptualized by enumeration than by location and diameter. Thus, kilocytomas, megacytomas, gigacytomas, and teracytomas indicate the successive 3-log orders of magnitude from $10^3$ to $10^{12}$ cells in a single mass, and gigacytosis, for example, indicates a total of one billion cells in the body (8). The strategy of achieving total cell kill, or at least tumor eradication to the level preventing its reappearance, can be contemplated more readily from such a mind set.

We have entered upon the high plateau of the new cancer therapeutics. The recognition of qualitative differences between cancer cells and normal cells—activated oncogenes, amplified or mutated receptors, telomerase, and absent or mutated tumor suppressor genes, for example—has set the stage for wholly new chemotherapeutic, immunological, and biological therapies for cancer. I for one look for unfettered exploration of these new approaches by constructively discontented investigators. I would forego all efforts that promised to inch along. I would expect randomized controlled trials to confirm modest gains in some partially treatable tumors. But I would hope that a few intrepid clinicians might make a quantum leap in such diseases as advanced lung cancer, mesothelioma, metastatic pancreatic cancer, metastatic melanoma, hormone-refractory prostate cancer, or metastatic renal cancer. The consistency of fatal outcome in finite time for these cancers would make a radical departure easily recognizable. It may be, however, that the first evidence of curative impact will only be seen after surgical bulk reduction, even to the point of no clinically detectable tumor. For comparison of disease-free intervals, randomized controlled trials may be required to show a subtractive effect of another therapeutic modality combined with surgery.

If the outcome of this approach were the evaluation of a larger number, among the infinite combinations of therapies that could be conceived, we are more likely to identify better therapies sooner than by looking at a lesser number over a longer time. Abandoning an unpromising lead is easier in an exploratory study than it is in a randomized trial. The good clinical cancer investigator is, after all, impatient to change the status quo for the better. Dr. Emil J Freireich is such a man. He unhesitatingly attacked the status quo ante, with results that made cancer therapy better for our patients and for us all.

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