

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Importance of Randomization in Early Clinical Trials

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H&O What are the main advantages/disadvantages of randomization in early clinical trials?

DS The single dominant advantage of randomization is the presence of a concurrent control group that allows for a fair, accurate, and robust assessment of the activity of the investigational agent or combination of agents. The challenge in nonrandomized single-arm studies where an agent is being compared to a historical control is that, with advances in technology in tumor imaging and supportive care, researchers are not able to predict what the studied endpoints in the new trial would be if a standard treatment was administered. Investigators also do not know if the population in their new single-arm trials is similar to the population in a previous trial; the previous trial could have been conducted in a specialized academic medical center or the new trial could be performed in a specialized academic medical center, whereas the original data are based on a multicenter community trial. It has been repeatedly demonstrated that outcomes differ between academic medical centers and community hospitals; there are numerous examples of agents that appear to have promising results in a phase II setting, but produce very different outcomes when taken to a phase III trial. Thus, the historical control data that are used to decide whether or not to proceed to a phase III trial are in most cases not sufficiently robust to allow an accurate determination of the true activity of the new agent.

The other element is that so many of our diseases are now being substratified by molecular markers, for example by KRAS mutation status, in colon cancer. Even if the historical dataset provided good information on the response rate in overall colon cancer patients, there is very

little data on the response rate or progression-free survival (PFS) in KRAS wild-type and mutated patients separately. As tumors become increasingly molecularly stratified, the historical data currently available will become considerably less robust because we are not going to know what is the expected outcome of these patients, particularly the molecularly stratified subgroups.

Because randomized phase III pivotal trials cost 10 to 100 million dollars, involve hundreds if not thousands of patients, and take many years to complete, it is crucial for investigators to ensure that there is strong data to support the initiation of such trials. In the absence of randomization in a phase II study, I do not believe that you can obtain data that will accurately predict how well the new regimen will perform against a concurrent control in the same population.

One of the downsides of early randomization is the larger sample size; typically the sample size is approximately twice as large, but could be as much as 3 times as large as is required in a single-arm phase II trial. These studies are therefore more costly and take longer to complete. Although there are disadvantages, I believe they are offset when one takes into account the enormous cost, both financial and opportunity, involved in an unsuccessful phase III trial.

H&O What role does randomization play in oncology trials?

DS Randomization is playing an increasingly critical role in oncology trials today because of the shift in endpoints in the phase II setting. The historical standard endpoint for a phase II single-arm trial was tumor response. In that setting, a single-arm trial was justifiable in many

cases because of the fact that tumors do not shrink by themselves—if an agent caused tumor shrinkage, that was a clear signal that it had efficacy. However, many of the newer agents today are cytostatic agents and thus are not expected to induce response. Another reason for the shift is that it has been recognized in multiple tumor sites, including advanced colorectal cancer and non-small cell lung cancer, that patients who experience long-term stable disease are receiving a benefit of therapy. For these 2 reasons, many phase II trials are shifting to a PFS-type of endpoint, which is often assessed at a certain time point (ie, 6 months). With this type of design, the concurrent control is much more critical because some tumors are more aggressive and others are less—some tumors will not grow in 6 months regardless of whether or not they are treated. Therefore, the fact that researchers are measuring an endpoint that in some ways is less sensitive to a direct antitumor effect, or is less able to clearly distinguish a direct antitumor effect from a less aggressive tumor, requires a need for randomization so that the PFS rate can be compared between the patients on a control therapy and those on the investigational drug.

H&O What are some important aspects of randomization?

DS Whenever possible, a double-blind trial would be preferable because at times PFS may be subject to investigator bias. It is a subjective measure; tests and various scans have to be read and repeated by investigators. There is always a possibility, particularly in a trial with a cross-over element, that investigators might call progression earlier on a control patient if they have the ability to cross the patient over to the experimental treatment because, naturally, they are excited about the possibility of patient benefit on the experimental treatment. Another factor is stratification—stratifying phase II randomized trials for 2–4 prognostic factors is important because in these smaller trials, the possibility of a chance imbalance in randomization is increased. Another aspect that is important in randomized trials is doing a 3-arm trial instead of a 2-arm. In a 3-arm trial, the control is compared to 2 different dose levels or schedules of the regimen. What sometimes happens is when researchers get to phase III trials, they realize they did not count the dose correctly or did not get the schedule quite right. Therefore, if possible, I would recommend initiating a randomized phase II trials with 3 arms and including an interim analysis or some within-trial adaptation. This would enable investigators to analyze the data halfway through the study, decide which of the experimental regimens might be more promising, and then eliminate one of the arms and continue with a 2-arm trial.

H&O Are there instances where a randomized design should not be used? If so, what are they?

DS I believe there is a place for both single-arm non-randomized trials and randomized trials. Single-arm trials can be very useful in initial exploration of activity, particularly if the agent is expected to be a response-inducing agent. A small single-arm trial can be effective prior to a randomized phase II trial to demonstrate that there is some chance of efficacy with the experimental agent. Also, a single-arm trial would be appropriate in last-line or refractory settings where there is no available therapy and any signal at all would be sufficient to proceed with the investigational drug, as it is often difficult to randomize best supportive care.

I believe that the optimal scenario would include conducting a small single-arm phase IIa trial (approximately 30 patients) right after a phase I study, which will provide better data on the pharmacokinetics of the agent and may be able to demonstrate activity based on biologic correlates. Following the phase IIa trial, it is best to perform a phase IIb trial enrolling 80–120 patients to obtain more evidence of activity, and then proceeding to phase III if appropriate.

H&O What do we hope to achieve by using randomization in earlier trials?

DS The goal is to minimize the number of phase III trials that fail to achieve success on the primary endpoint. Presently, approximately 25% of phase III trials are successful in terms of hitting their primary endpoint. Many researchers feel that this percentage is unacceptably low and that huge amounts of money are spent on phase III trials that are missing the preliminary data necessary to help increase the rate of success. The objective of using randomization in the phase II setting is to increase the success rate, which would save clinical oncology research hundreds of millions of dollars yearly and would more effectively optimize the use of patients so that there isn't an opportunity loss associated with entering a negative phase III trial. By obtaining robust data in the randomized phase II setting where there is a concurrent control, we can say with greater confidence that it is due to the agent and not some population variation or shift in imaging technology.

H&O Can you discuss the highlights of the article you published on optimizing the design of phase II trials?

DS One of the things discussed in the paper is the 3 sources of error introduced in single-arm phase II trials

relative to a randomized phase II trial. The first is that when typically designing a single-arm phase II trial, we do not recognize that our estimate of the historical success rate has error associated with it. We do not really know the true historical success rate; even in large randomized phase III trials there is a confidence interval around the specific rate. Because we assume that the rate is precisely 35%, for example, when in fact it is not, this automatically makes our single-arm phase II trials overly optimistic. The second point is that phase II single-arm trials, because they do not require a large population, are often done in single centers, specifically academic medical centers. We know that patient outcomes in those centers differ from outcomes in multicenter trials in a community setting, and thus, it is inaccurate to assume that the experience of a single-arm study will translate to the wide scenario that is employed in a phase III study. The third error deals with shifts in patient population over time. For example, data from a large randomized phase III trial conducted in the 1990s or early 2000s may not accurately predict what that same regimen may do in 2009. This is because over time there has been an emergence of better supportive care for patients, better

patient selection, stage migration and bias, differences in imaging technologies with new positron emission tomography and computed tomography scans, and differences in what constitutes response.

This is an area of interest and there is a considerable amount of ongoing research. My group, the North Central Cancer Group, has been doing clinical trials for 30 years and has enrolled over 60,000 patients to clinical trials; we have a great database both of single-arm and randomized phase II trials. In many diseases, we have moved to preferring the randomized phase II design, but what we are doing is going back to our experience of both single-arm and randomized phase II trials and trying to understand the circumstances when each might be appropriate. We look forward to presenting this work at upcoming meetings.

Suggested Readings

Ratain MJ, Sargent DJ. Optimising the design of phase II oncology trials: the importance of randomisation. *Eur J Cancer*. 2009;45:275-80.

Rubinstein L, Crowley J, Ivy P, Leblanc M, Sargent D. Randomized Phase II Designs. *Clin Cancer Res*. 2009;15:1883-1890.

Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol*. 2005;23:7199-7206.