

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Translational Research in the National Cancer Institute's Cooperative Groups



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H&O What is the Alliance for Clinical Trials in Oncology?

WFS The Alliance for Clinical Trials in Oncology, which works with the National Cancer Institute's (NCI's) National Clinical Trials Network, is a multidisciplinary combination of 3 previously independent cooperative groups.

The program is made of 5 separate groups: the Office of the Group Chair, the Statistics and Data Management Program, the Central Protocol Operations Program, the Translational Research Program, the Cancer Control Program, and the American College of Surgeons Clinical Research Program. Essentially, the Alliance is a collection of several organizations with the same goal, which is to reduce the impact of cancer through clinical trials, basic research, and translating advancements into practical use.

One approach we take is to make use of existing material from previously completed clinical trials. When a new scientific question is asked that relates to extant samples from an older clinical trial, we create a secondary-use protocol so that those samples can be used again. For the prospective component, we are finding ways to integrate tests that are still somewhat exploratory but are deemed potentially important into the trial design. The test is being used as part of the clinical trial, even as it is also being validated by the study.

H&O What is the Translational Research Program?

WFS The Translational Research Program is dedicated to advancing the integration of pharmacogenomics and other tests into clinical care, with the goal of honing treatment strategies. The program is focused on molecularly driven oncology; in particular, on the optimal integration of this research into the clinical trials being spearheaded by the Alliance.

We have an increasing body of evidence about the link between various genetic variants and drug efficacy, for example. There is a pressing need to make more practical use of the tests and assays we have so that we can make better treatment decisions.

H&O What is new about the Translational Research Program?

WFS With all attempts to advance the way we research new cancer treatments, there is always something old and something new. One of the innovative aspects of this program is the integration of translational diagnostics into the primary and secondary endpoints of current clinical trials.

Many trials now require that samples collected from patients undergo a particular laboratory test. As a result, we have data on the accuracy or clinical utility

of the test in the context of the new treatment being investigated in the study.

Ten or so years ago, we had few examples of this approach. Translational programs were focused on secondary-use protocols, querying existing samples with some test or assay to see if it might be useful to examine in a correlative study. Sometimes these correlative studies had a narrow focus, and sometimes they were more broadly applicable. The question asked was not always directly relevant to treatments being used at the time. The information gleaned may have provided an insight about the stage of the disease or about treatment in general, but it did not necessarily provide anything immediately useful for the patient in the clinic.

Today, these tests and assays are being incorporated into clinical trials. A test may be used to determine trial eligibility, for example. The translational components have reached a point at which they are just as important as the therapeutic question being evaluated.

H&O Are there enough data on enough genetic variants to take this approach with many clinical trials?

WFS Sometimes there are enough data and sometimes there is enough belief. The decision about when to include a test for a particular variant or other marker in a study can be difficult. We may look back in a few years and wonder why we thought a certain test should be included, or we may see that we missed an opportunity to validate a test years earlier. We may question why we believed what we did at the time.

However, the purpose of clinical trials is to push the frontiers of scientific knowledge. We have to balance the need to be rigorous and analytical with the fact that waiting for rigorous data can delay progress substantially.

Sometimes there is a strong scientific rationale for believing that a particular variant or marker will be a strong driver of response or resistance to a particular treatment, and that inclusion of a particular targeted therapy into the treatment regimen will reverse resistance. And we do have some examples of resounding success, in which the rationale proved correct and changed clinical decision-making.

But the biology of cancer is incredibly complex, which means the importance of a particular variant or test will likely be very heterogeneous. Sometimes there are just enough data to tip us toward giving something a try in a clinical trial setting. Or there may be such strong evidence about the prognostic utility of a test in an early-stage clinical trial that we can move it into routine care sooner.

Another issue that frequently arises is whether a test should be used for patients with all stages of a particular

cancer. Can we apply what we have observed in early-stage disease to advanced-stage cancer? If doing so could reduce the amount of treatment, which could in turn reduce toxicity, should we explore use of the test in an advanced-stage setting even if the data seem preliminary? Sometimes it is reasonable to use common sense to move an investigation forward rather than waiting for more rigorous data.

H&O How can you obtain the necessary data on already approved treatments?

WFS We have to develop a system that allows us to study the use of biomarkers for treatments that are already part of routine clinical practice, knowing that we can never go back 15 years to prospectively validate their use. In clinical trials today, the principal objective will always be to validate the therapy, with the validity of diagnostics and biomarkers taking a back seat. But there has to be room to work on a case-by-case basis, to formulate trials in the way that will best serve our learning and advancement of treatments.

H&O Most advanced-stage clinical trials are funded, at least in part, by the pharmaceutical industry. Are private companies also interested in fast-forwarding the integration of biomarker tests into trials and routine use?

WFS Early on, there was some concern that private companies might resist this direction for clinical trials. But there are very compelling examples of how all parties win when this kind of trial is a success.

Approximately 20% of US women with breast cancer have a *HER2* mutation. Let us say that therapy targeted at the human epidermal growth factor receptor 2 (*HER2*) protein can improve survival for approximately 50% of the women in this population. In other words, 10% of all breast cancer patients would be likely to benefit.

There are treatments that have had a 10% response rate among the general disease population, in which a biomarker like *HER2* is not known or not relevant. Such drugs have not always found a place within the standard of care.

The presence of a biomarker changes that scenario. The overall impact is the same, but there is a strong negative predictive value and a reasonably good positive predictive value. A drug that benefits 50% of the correct population is profoundly important.

It is better for a pharmaceutical company to have a blockbuster in the correct segment of the population than to have a drug with an overall weak response because there is no information on what subpopulation might be most appropriate for it.

H&O So it is better to have a big “yes” for fewer people than a “maybe” for a lot of people?

WFS Absolutely. This scenario is better for patients, for physicians, for clinical trial investigators, for industry, and for the NCI.

H&O How could the incorporation of biomarker tests into clinical trials affect the time frame for bringing a beneficial drug to market?

WFS With statistical analyses of clinical trial data, we examine the relative difference in response between 2 groups. If a subset of patients has an aggressive form of the disease at hand, and an experimental treatment has a profound impact on that subset, the relative difference in survival or response rate will be large. As a result, the cost and duration of the trial are reduced. In addition, the advancement is more important.

In breast cancer, the ability of neoadjuvant therapy to markedly reduce disease is a strong predictor of 5-year survival. So response to neoadjuvant therapy, particularly among patients with stage II or stage III disease, can be used as a surrogate endpoint for trials in which treatment is given before surgery. The pathologic response can be measured during surgery as the initial endpoint. An improvement in survival would still need to be demonstrated subsequently. The US Food and Drug Administration (FDA) has provided guidance on the use of the neoadjuvant trial model for accelerated initial approval of new therapies in breast cancer, with at least one therapy granted FDA approval under this program thus far.

H&O What challenges is the program currently facing and how are you as director approaching these challenges?

WFS One challenge is that we are facing a very difficult economic time for clinical research—for all research, really. When it comes to getting translational science approved and funded, we are in dire straits. As I mentioned earlier, biomarkers and diagnostic tests are still considered secondary in importance to the therapeutic question being asked. The translational scientific community does not have an accessible structure for bringing diagnostics to the highest levels of clinical utility across the country. The pharmaceutical industry is then faced with having to provide all the funding in order for their products to have an impact.

For academic researchers—the biomarker developers, essentially—there is nowhere to turn. The process of obtaining funding is extremely slow, and the chances of being funded are extremely slim. These biomarker tests end up being pushed out of clinical trial protocols because the funding is not available. The NCI does provide funding for biomarker studies, but it is limited. The biomarker has to be necessary for determining patient eligibility, for example.

For the academic investigator working on a potentially important biomarker, the difficulty in securing resources is a huge mountain to climb. Yet as we move toward precision medicine with a diagnostic-driven personalized approach, we need to fund the critical final steps of biomarker development.

Right now, one of my main priorities is to get the diagnostic community in academia and industry engaged with the government and cooperative groups in order to bring more valuable diagnostics into patient care faster.