Redefining Clinical Trials: The Age of Personalized Medicine

The triumph of personalized cancer therapeutics in recent years is prompting some oncologists to rethink clinical trial design; other researchers have different priorities for trial reform.

As Hiroyuki Mano entered the oncology ward at Seoul National University Hospital, he was amazed to see his patient walking around, asking people to recommend the best local restaurant. Just days before, the patient had been hooked up to oxygen monitors. Cancer had spread rapidly through his lung, making it difficult to breathe and swallow. He had been air-lifted from Japan to Korea to get access to a clinical trial that was testing a new drug, crizotinib.

The crizotinib trial was unusual because it did not contain a control arm for placebo treatment. In 2008, Mano and his colleagues at Jichi Medical University identified a fusion protein of anaplastic lymphoma kinase (ALK) with another protein EML4, resulting from a chromosomal rearrangement seen in about 4% of lung cancer patients. The ALK-EML4 fusion is a powerful driver of cancer but is potently inhibited by crizotinib.

In this trial, doctors only enrolled patients testing positive for the ALK biomarker. Crizotinib treatment resulted in dramatic shrinkage of the tumors, visibly and almost immediately, in some cases within 48 hr. There could be no doubt that the drug was working. Even though only 82 patients were enrolled, the results were clearly statistically significant. Dr Mano’s patient was on his feet in days.

**Trials on Trial**
Beyond its immediate life-saving effects, crizotinib and other recently approved targeted therapeutics have changed the landscape of oncology: clinicians are rethinking the traditional model of randomized controlled trials (RCTs) for the era of personalized medicine.

RCTs are structured in four phases: The first is a dose-response phase to find out how much of a drug can be safely tolerated by patients. The second step is an escalation phase, where more patients are enrolled, and the efficacy of the drug is gauged. Many drugs that seem extremely promising in the lab fail by phase II. If they do succeed, the drugs enter phase III, where higher numbers of patients are enrolled, and the drug is compared with the standard regimen. The final phase is a post-marketing phase that continues after a drug has been licensed in order to study long-term effects.

Usually, clinical trials enroll a large number of patients to show that a drug’s effects are statistically significant. Patients are randomly assigned to a placebo or a drug arm, and neither the doctor nor the patient knows which group they are in. Such trials are described as being randomized and double-blind.

However, it has become apparent that most drugs that seem extremely promising in the lab fail in the clinic. Because of this, many have suggested that trials ought to be restructured to get a quicker “yes or no” answer before millions of dollars and often a decade of effort are sunk in getting an unsuccessful drug through the early phases. Crizotinib, especially, has given weight to this argument: it took just 2 years to get FDA approval—among the fastest in known history. The success is indicative of the power of personalized medicine at its best.
In addition, ethical concerns about trial structure have surfaced, including whether it is morally right to give a placebo, or standard-of-care drug. Some oncologists believe that this question of ethics is especially valid in personalized medicine, where the postulate is that all patients with the relevant genetic lesion, or biomarker, will respond to the drug.

In other diseases, however, it has been more difficult for researchers to identify genetic markers that predict a patient’s response to a drug. How to improve trial design in these cases is less clear.

**The Exception or the Rule?**

One of the few successes in pharmacogenetics has been with hepatitis C, where David Goldstein, director of the Center for Human Genome Variation at Duke University, and his colleagues identified an allele that predicts whether or not a patient with hepatitis C will respond to standard-of-care treatment.

“I think it is entirely possible that in a number of therapeutic areas, we will be able to subdivide patients into genetic subgroups that influence their responses to treatments, but we just don’t have many examples right now,” says Goldstein.

Genome-wide association studies (GWAS) have been heralded as a powerful tool to identify genetic variance underlying human disease, but success has so far been mixed. The vast numbers of rare and “private” mutations that could be responsible for individual responses to treatment have confounded many efforts to identify useful new biomarkers.

“GWAS have most certainly not given us a way to meaningfully partition patients in the context of clinical trials,” says Goldstein.

So although promising results in hepatitis C and cancer could well indicate that patient response in other diseases is similarly governed by genetics, researchers just do not have the data yet to prove or disprove this theory. Biomarkers for most diseases remain elusive.

**The Hunt for Better Biomarkers**

“Many biomarkers people want to look at are not binary; they are not a yes/no when you run the test,” says Stuart Lutzker, vice president of biooncology exploratory clinical development at Genentech.

Robert Califf, vice chancellor for clinical research at the Duke Translational Medicine Institute, agrees: “The vast majority of biomarkers are not accurate for whether or not treatment will work. That is why they are biomarkers and not surrogates.”

And even if a clear biomarker is present, clinicians cannot usually waive a control arm as in the crizotinib trial. Crizotinib caused dramatic tumor shrinkage, leaving no doubt of its potency, but most drugs simply pause cancer growth. The only way to judge a drug’s effect in such cases is by comparing against patients who have been given a placebo or standard-of-care treatment.

Califf and colleagues are part of the Clinical Trials Transformation Initiative, which has been tasked by the FDA to reform clinical trials. The rethink is not driven by the hope of personalized medicine, says Califf. Rather, he says, they are trying to streamline trials in order to reduce the immense costs and high rates of failure.

Nonetheless, at least in the field of oncology, clinicians believe that the reform ought to go further, and patients should be selected for trials with their genetic makeup known from the very start. This call for prescreening contrasts with how trials are typically conducted. Investigators usually enroll a large number of patients, and once the trial has begun, they may do a retrospective genetic analysis on some of them.

**Personalized Drug Discovery**

If the hypothesis is extended backward into the drug discovery phase where researchers administer drugs to tumor-derived human cell lines, it suggests that only a small fraction of the cell lines would respond to any given drug. Many drugs could be getting ruled out unnecessarily as inactive before they even reach the clinic.

Daniel Haber at the Massachusetts General Hospital and his colleagues suggest that an ideal human tumor cell line profiling panel should consist of between 2,000 and 6,000 cell lines. However, there are only between 1,500 and 2,000 tumor-derived cell lines available in total today.

It is also important to detail the molecular pathways through which a drug halts a tumor in order to identify new targets once the cancer becomes resistant to the drug in patients. Crizotinib, for example, extends life by 6 months to a year, but eventually the cancer resurges. Haber suggests that this level of detailed ongoing analysis should be the standard for well-designed clinical trials and calls for basic researchers to be directly involved in trials from start to finish.

Ira Mellman, vice president of oncology at Genentech, would also like to see greater collaboration. His view is that the best model for human cancer is human cancer. He declares that there is a moral imperative to get as much information as possible from patients, as early as enrollment for phase I.

“No patient is making a sacrifice in order to participate in these trials, especially when a drug is entirely experimental and we have no evidence the drug is going to work,” says Mellman. “We have to recognize that as a sacred trust.”

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DOI 10.1016/j.cell.2012.02.041