Personalized-Medicine Trials on the Rise

By Steven Benowitz

Although targeted therapies—based on the molecular profiles of patients’ tumors—rather than treating cancer according to its organ of origin may sound like a beautiful theory, the successes of early-stage clinical trials are putting them closer to the clinical roadmap of oncology treatments.

A study presented at the American Society of Clinical Oncology in 2011 found that matching advanced cancer patients in phase I trials with targeted drugs on the basis of the molecular profiles of the patients’ tumors—rather than on the tumor site—resulted in longer survival, a longer time before treatment became ineffective, and better response rates than treating patients without molecular matching. By targeting drugs at identified genetic and molecular aberrations, researchers found a 27% response rate, compared with 5% who were unmatched, according to principal investigator Apostolia-Maria Tsimberidou, M.D., Ph.D., an associate professor in the Department of Investigational Cancer Therapeutics at the University of Texas M.D. Anderson Cancer Center in Houston.

“It’s one of the early studies exploring personalized medicine, and impressive in terms of the number of patients,” said Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology and Urology and a Howard Hughes Medical Institute investigator at the University of Michigan. “They are focused on a small number of mutations that are all well known, and in some cases, there are targeted therapies available. While they are not looking at the entire mutational landscape, I applaud them in paving the way for these types of efforts. It is a great proof of concept.”

**Setting a Precedent**

Another study presented at the 2011 American Society of Clinical Oncology meeting involved a new 14-institution lung cancer consortium based on a similar approach, testing advanced lung cancer patients for specific “driver mutations” to help physicians tailor their therapies. The consortium tested more than 1,000 newly diagnosed stage IV lung cancer patients whose cancer had returned after initial treatment for evidence of mutations and abnormalities in genes such as KRAS, EGFR, and ALK. The initial results showed that one of 10 such genetic mutations or aberrations were detected in 54% of 516 lung cancer patients tested at diagnosis, enabling doctors to either find the most appropriate drug or consider enrollment in a clinical trial.

According to Richard Schilsky, M.D., professor of medicine at the University of Chicago and deputy director of the University of Chicago Comprehensive Cancer Center, stories abound involving patients with advanced cancer who had their tumors profiled, finding unexpected mutations leading to successful therapies. “These are powerful stories because they prove the same principle. If you find the gene or group of genes that is driving cancer progression, and interrupt that in some way, you can make a big difference,” Schilsky said.

**Programs Broadly Focused**

A host of programs at academic medical centers are also focused on bringing personalized medicine closer to the clinic. At Massachusetts General Hospital in Boston, researchers developed a 15-gene panel of key oncogenic drivers, such as RAS, BRAF, PI3 kinase, and EGFR. “We developed the assay to test simultaneously in all the patients where the doctor thinks that it might be important for a standard treatment decision or in the context of participation in a clinical trial,” explained Leif Ellisen, M.D., Ph.D., associate professor of medicine at Harvard Medical School and codirector of the Translational Research Laboratory at Massachusetts General.

According to Ellisen, most advanced cancer patients at Mass General receive this screening when “the patient’s physician thinks it could make a difference in how their patient could be treated and we want to see if the patient could be a candidate for a targeted-therapy clinical trial.

“This approach allowed us to expand our phase I program and has allowed us to do the sorts of trials directed by the genotype but not the disease,” he said. “We have made some surprise findings with these rare subsets of patients with mutations and oncogenes you wouldn’t expect in a particular disease.”

Other institutions are adopting this concept in different ways, he noted. “Once this type of program is instituted more broadly, the question is how complex the picture will be. We know a lot about a handful of cancer driver genes, but when we start looking more broadly at not just a couple of dozen genes, but perhaps hundreds, it will test our ability to apply therapies rationally.”

At the Vanderbilt–Ingram Cancer Center in Nashville, Tenn., specialists routinely test tumors from patients with non–small-cell lung cancer, melanoma, breast cancer, and colon cancer for multiple...
Challenges Remain

For all the promise of these nascent personalized-medicine approaches, they have problems and challenges, which can be both limiting and frustrating.

“Oftentimes, we can’t find that key mutation, or the specimen isn’t good enough, or the mutations weren’t actionable with a drug, or there wasn’t an available trial,” said Schilsky. “It can be a difficult approach, and there are skeptics. But at the same time, it can also be a very productive approach, though it won’t help every patient. I’ve sent specimens to pathology and they’ve come back without any identified mutation or target.”

Ellisen believes that drug resistance will become an important issue, as more tumor heterogeneity is seen. “That is going to be the key challenge to overcome in the setting of targeted therapy, where currently we have mostly single pathway–targeted agents. The question is, what is going to be the most effective combinations of targeted agents?”

He suggested that clinical trials will increasingly emphasize treatments that target tumor genotypes and pathways, along with the site of the cancer. “What might happen is that phase I trials could be stratified,” he said. “Instead of just being a toxicity trial for a number of cancers, patients could be selected and stratified as possible responders. There may be some indication how the genotype interacts with the disease type.

“We think we are moving out of the era of trials of thousands of unselected patients with drugs with which we are unsure who will benefit and into a new era where things are more selective,” he said. “We can make a difference in figuring out in real time which new drugs coming along are the best applications. There is tremendous promise for centers to do translational medicine in addition to the traditional therapies.”

© Oxford University Press 2012. DOI:10.1093/jnci/djs432