Enrolling Patients Into Genomically Matched Clinical Trials Found Challenging

A recent study has shown that multiplexed genomic profiling of patients’ tumors can be broadly implemented. However, few patients with actionable mutations currently are enrolled into clinical trials to receive genotype-matched therapy (J Clin Oncol [published online ahead of print May 26, 2015]. pii: JCO.2014.60.4165).

Next-generation sequencing has become increasingly available for patients with all tumor types, but the results are sometimes difficult to act on for various reasons, including the lack of drug availability for a particular tumor type or the lack of an available clinical trial.

“Our trial shows that potentially actionable genomic alterations are common across a variety of tumor types and that significant clinical trial infrastructure needs to be built to optimally utilize genomic testing through trial enrollment,” says Funda Meric-Bernstam, MD, medical director at the Khalifa Institute for Personalized Cancer Therapy and chair of the department of investigational cancer therapeutics, both at The University of Texas MD Anderson Cancer Center (MDACC) in Houston.

Dr. Meric-Bernstam and her colleagues reported on the first 2000 patients enrolled into their trial. Patients could have any type of malignancy and physicians could enroll patients they believed would benefit from genomic profiling and were likely to consider a therapeutic trial. Most patients had metastatic, inoperable locally advanced or locally recurrent disease. Patients who had diseases for which genomic profiling is standard, such as lung cancer, were usually tested without trial enrollment, and therefore were underrepresented in this study.

From March 2012 to July 2013, a total of 2601 patients were enrolled. Of these, tumors from 601 individuals were not tested because of inadequate tissue or DNA quantity or quality. Of the 2000 patients undergoing genomic profiling, 789 (39%) had at least 1 mutation in a potentially actionable gene, meaning an alteration for which an established or investigational targeted agent exists. Some 414 patients (21%) were found to have a somatic mutation that was not actionable, 205 patients (10%) had a likely germline variant, and 592 patients (30%) had no mutations identified. Of the patients studied, 145 (7.3%) had 2 or more potentially actionable alterations identified.

Among the 789 patients with possibly actionable alterations, 83 (11%) enrolled in genotype-matched clinical trials: 7% on a trial that required a particular mutation for eligibility and 4% on a genotype-relevant trial (genotype-
relevant indicates that the biomarker was not necessary for enrollment but the therapeutic agent targeted the gene product or downstream signaling. A total of 121 of these 789 patients (15%) went on to take part in other clinical trials.

To investigate barriers to trial enrollment, the researchers reviewed the records of 429 patients with PIK3CA/AKT1/PTEN/BRAF mutations. They found that 75 patients (17%) did not return to the investigators’ institution after testing, 55 patients (13%) returned but were then treated at a different institution, 26 patients (6%) did not receive further treatment after testing because of declining performance status, and 43 patients (10%) did not initiate new treatment for other reasons such as stable disease. Of the remaining 230 patients who did receive their next treatment at MDACC, 40 (17%) were on genotype-selected trials, 16 (7%) were treated on genotype-relevant trials, and 40 (17%) received a genotype-relevant drug off study.

“Genomically matched trials are inherently appealing to patients and physicians, but are challenging because of multiple issues, including the potential need for another biopsy if there is not adequate tissue to test, requiring a closer collaboration between medical oncologists, pathologists, and interventional radiologists than is typical,” says Jeffery Abrams, MD, acting director for clinical research and associate director of the Cancer Therapy Evaluation Program at the National Cancer Institute (NCI) in Rockville, Maryland. “Also, greater coordination among clinicians and the research community (public and private) is needed because the greater precision results in dividing even common tumors into smaller subsets for research, and those studies can rarely be accomplished at a single center.”

**Barriers Identified**

Several challenges were identified that hindered the ability of the researchers to enroll patients in genomically driven trials. It is interesting to note that 17% of patients did not return to MDACC after testing and 13% wanted treatment closer to home, so that in nearly one-third of patients, genomic testing likely was not used for therapy planning.

The authors state that one way to mitigate this is to test only local patients, although that would make the consultations less informative. However, carefully assessing a patient’s interest in trials before testing may help. In addition, 6% of patients could not participate in trials or tolerate further therapy because of a decline in their performance status. Therefore, the authors recommend that patients should be carefully assessed for their ability to tolerate new treatments before genomic profiling is performed. Furthermore, many of the patients on the trial underwent genomic profiling to help with future treatment planning, but not necessarily point-of-care testing for the next line of therapy, which may account for some lost patients. However, even in past studies that are point-of-care for next-line therapy, such as the Lung Cancer Mutation Consortium, a minority of patients were enrolled on matched studies. In one such study, 64% of patients had a relevant actionable mutation identified, but only 28% were enrolled on a marker-selected trial (JAMA. 2014;311:1998-2006).

Another obstacle was simply the lack of an appropriate trial, but over the study period the number of available trials increased. At MDACC, researchers have used their genomic testing results to design investigator-initiated trials, added some industry-sponsored trials, and initiated basket-type trials that enroll patients based on mutation status rather than tumor site and histology. Nevertheless, investigators have called for novel approaches in trial design to improve enrollment.

“To increase enrollment in trials, widened access to investigational agents through multicenter trials, including efforts by both the NCI (National Cancer Institute), academic partnerships, as well as innovative industry solutions, is occurring,” says Dr. Meric-Bernstam.

“Equally important is to provide decision support for interpretation of the genomic data and actionability of specific variants found, and their therapeutic implications and relevant trials available,” she adds. To that end, researchers at MDACC have developed an easy-to-search Web site (Personalizedtherapy.org) that integrates information regarding multiple actionable mutations, including basic scientific information as well as available targeted drugs and trials. “The NCI is very focused on precision medicine and is launching the NCI-MATCH (Molecular Analysis for Therapy Choice) study,” says Dr. Abrams. “This study is not restricted by tumor type and it is available to any adult patient with a solid tumor or lymphoma whose tumor has progressed on standard treatment. Most importantly, NCI has been able to collaborate with many drug companies so that a large number of targeted agents will be available to hopefully match patients’ mutations to available drugs. This may help to overcome some of the concerns expressed in the current article.”

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