Precision Medicine for Pediatric Cancer

In likely the first study of its kind in children, researchers used genomic sequencing data from patients’ advanced and rare cancers to suggest effective treatment options. The findings demonstrate the feasibility of incorporating genomic information into the clinical management of pediatric patients.

In the single-site, observational study, 91 children and young adults with relapsed, refractory, or rare cancers underwent whole-exome and transcriptome sequencing. The data were then interpreted and analyzed by a tumor board made up of oncologists, geneticists, and other experts. Actionable findings were reported for 42 of the patients—including 15 of 28 patients with hematologic malignancies and 27 of 63 with solid tumors. Based on the data, physicians changed the treatment for 14 patients, nine of whom went into partial or complete remission (JAMA 2015;314:913–25).

“This is one of the first comprehensive DNA/RNA sequencing platforms implemented in pediatric patients with advanced cancer,” says the study’s senior author, Arul Chinnaiyan, MD, PhD, director of the Michigan Center for Translational Pathology at the University of Michigan in Ann Arbor. “We showed that it is possible to carry this out in a regimented fashion and to impact the individual management of patients in terms of the potential clinical use of targeted therapeutic agents.”

Investigators defined actionable findings as somatic mutations targetable with an alternative therapy; molecular aberrations leading to changes in a patient’s diagnosis; or cancer-related germline mutations that could inform genetic counseling.

However, many patients with actionable findings experienced tumor progression before the results could be acted upon, partly due to the time it took to convene the tumor board and interpret the findings. The median time from biopsy to sequencing analysis and treatment recommendations was more than 6 weeks.

Access to targeted therapies was another limiting factor, says Chinnaiyan.

In some cases, patients with potentially actionable mutations could not access treatment due to exclusion criteria for a clinical trial or lack of pediatric dosing information for a drug approved for adults.

“The pediatric oncology community will need to completely rethink models of drug development in the genomic era as rare diseases become even more rare based on genetically defined subsets,” notes an accompanying editorial (JAMA 2015;314:881–3). “Academic, federal, and industry leaders must overcome the current risk-aversion mentality that interferes with translational innovation and develop new mechanisms to more deftly develop and deliver drugs to children with cancer.”

The study has several limitations, the authors acknowledged, including lack of a control group to distinguish whether treatment changes based on the study actually improved outcomes compared with standard of care. In addition, because some tumors were sequenced from archival material, any new mutations that emerged during treatment would have been missed.

Although this study focused on patients with advanced cancer, the goal is to incorporate clinical sequencing earlier in the disease process, says Chinnaiyan.

“It’s exceedingly difficult to treat patients who have gone through many different therapeutic regimens because the tumor has developed so many resistance mechanisms,” he says. “Clinical sequencing efforts have the potential to improve clinical management if we can bring them in earlier in the course of cancer development.”

Researchers Win Coveted Lasker Awards

Three renowned scientists who made discoveries that advanced understanding of genetics and biology—and that led to the development of new cancer therapies—have been honored for their work with prestigious prizes from the Albert and Mary Lasker Foundation. Among the most coveted honors in medicine, the awards each carry an honorarium of $250,000.

Evelyn M. Witkin, PhD, professor emerita at Rutgers, The State University...
High-Affinity PD-1 Protein Has Potential

A small, engineered protein that selectively binds to PD-L1 was more effective in shrinking tumors and synergizing with other immunotherapies than conventional PD-L1 antibodies in a preclinical study, according to data presented at the CRI-CIMT-EATI-AACR International Cancer Immuno-therapy Conference in New York, NY, in September.

The high-affinity PD-1 protein may overcome some drawbacks of existing antibody-based immune checkpoint inhibitors, says study corresponding author Aaron Ring, an MD/PhD student at California’s Stanford University School of Medicine who will soon join the faculty at Yale University School of Medicine in New Haven, CT. “It is approximately 10 times smaller than an antibody and it lacks the antibody ‘Fc’ moiety that is recognized by Fc receptors on cells like macrophages,” he says. “Consequently, the high affinity PD-1 protein penetrates deeper into tumors and, unlike antibodies, does not cause unwanted depletion of PD-L1-positive T cells that mediate antitumor immunity.”

Ring and his colleagues used directed evolution to design the small protein. Using this technique, they first created a library of over 100,000,000 different PD-1 variants that they displayed on the surface of yeast. They then used magnetic and fluorescence cell sorting techniques to select for the tightest binders to recombinant PD-L1 protein. Through increasingly more difficult binding conditions, they zeroed in on one variant that bound to PD-L1 about 50,000 times more tightly than wild-type PD-1.

To assess its effectiveness in penetrating solid tumors compared with anti–PD-L1 antibodies and our high-affinity PD-1 protein penetrate tumors, and there was a striking difference,” says Ring. “The antibody is mostly found close to blood vessels and at the tumor periphery, whereas the smaller PD-1 protein spreads more extensively throughout the tumor.” They also found that the small protein was more effective at treating larger tumors than PD-L1 antibodies. Both therapies shrank tumors 50 mm³ in size, but only the small protein was effective against tumors measuring 150 mm³. Adding an anti-CTLA4 antibody to anti–PD-L1 therapy in the larger tumors did not improve the efficacy of anti–PD-L1, whereas combining an anti-CTLA4 antibody with the small protein resulted in greater efficacy compared with either treatment alone. “Our hypothesis is that as tumors grow larger, the need for effective penetration by the therapeutic agent becomes more important,” says Ring.

Several issues should be addressed before the high-affinity protein is ready for clinical testing, the researchers emphasize. For example, due to its small size, it is excreted from the body more quickly than antibodies, and
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