PRECISION MEDICINE ONLINE

Early Functional Precision Medicine Approaches Show Potential to Improve Patient Outcomes

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ORLANDO – Although functional precision medicine has the potential to transform cancer care, experts at the American Association for Cancer Research's annual meeting recounted how the present regulatory and reimbursement environment has made it difficult for them to use research findings to inform patient treatment.

Precision cancer medicine today largely involves identifying and therapeutically targeting genetic cancer drivers. Researchers and drugmakers have successfully used that model to bring many approved biomarker-driven targeted therapies to market. And yet, such therapies are only available for about 10 percent of cancer patients, and while some of these drugs extend survival in the advanced cancer setting, very few cure patients.

Experts in the field are trying to improve the efficacy of precision cancer therapies by targeting multiple cancer-driving or resistance biomarkers with combination treatment strategies, or by giving these drugs to patients with earlier-stage disease. Others are trying to bolster treatment efficacy using so-called functional precision medicine (FPM) approaches, which often entail adding on top of tumor genomic data tissue- and mechanism-agnostic information using tools such as drug sensitivity assays and single-cell sequencing tests.

Using FPM, researchers have been able to match patients to treatments and show improved outcomes on drugs that would not have been options based on tumor genomics alone. Alana Welm, senior director of basic science at the University of Utah's Huntsman Comprehensive Cancer Center, asserted that aside from high-profile successes in certain cancers, precision medicine "hasn't really been a game changer," because although cancer is driven by genetic mutations, other factors influence patients' responses to therapy. "There is epigenetic modulation that happens during therapy that leads to cellular plasticity, acquisition of resistance, and adaptation to therapy," said Welm. "We're here to talk about the next generation, which is where we combine information on the genotype of the tumor as well as its functional behavior."

Welm's laboratory studies advanced breast cancer and breast cancers at high risk of recurrence using patient-derived xenograft (PDX) models and tumor organoids grown either from PDXs or from the patient directly. She presented two examples of functional precision medicine studies conducted using these models at AACR. In each case her team faced systemic hurdles when delivering actionable information to patients.

In one study, researchers were testing their hypothesis that the ability of a patient's tumor to engraft and grow in a PDX model can be indicative of early recurrence in estrogen receptor (ER)-negative breast cancer. In addition to being developed into a PDX model, patients' tumor samples also underwent genomic profiling and were grown into an organoid for drug sensitivity testing.

The researchers observed a "remarkable correlation" between PDX engraftment and recurrence. However, Welm had mixed success in returning to patients information that could help guide subsequent treatment decisions.

In one case, a US Food and Drug Administration-approved breast cancer therapy, Novartis' Afinitor (everolimus), worked very well in organoids and produced stable disease in the PDX model. Afinitor is approved only for ER-positive breast cancer, so it is not a drug the physician in this case would have thought to prescribe to a patient with an ER-negative tumor. This patient had received standard neoadjuvant chemotherapy but had residual disease at the time of surgery, indicating she was at higher risk of recurrence. The patient went on to have radiation therapy, and when her breast cancer eventually recurred, her physician prescribed an unspecified standard-of-care, first-line therapy.

In the meantime, Welm worked with the institutional review board overseeing her research to get permission to return the assay results to the patient. She received IRB approval, but because the study was funded by the Department of Defense, she also had to go through an IRB process with that agency. "The process took months and months just to get a phone call, much less approval," said Welm. "Unfortunately, the patient did not receive [Afinitor], and she unfortunately died of breast cancer."

The two IRBs, however, subsequently allowed Welm to amend the trial protocol so investigators could return results to physicians who wanted to use them to guide treatment decision for patients who had exhausted standard-of-care options. However, there were other challenges, such as the efficacy of the drugs themselves, that limited the utility of the information gleaned from PDX models and organoid drug screening.

In another example, a patient in the trial had a cancer recurrence with liver metastases. The PDX model and organoid drug screening identified a therapy that her physician prescribed, and to which she had a complete response with all liver metastases eliminated. However, the patient's cancer recurred again six months later and she went on to die of breast cancer. "The problem here is we still don't have curative therapies in the metastatic breast cancer setting," said Welm.

Welm and her colleagues have now begun a new trial in HER2-negative metastatic breast cancer to determine the feasibility of providing personalized genomic and drug sensitivity information to patients and exploring how those results influence physicians' choices of next-line therapies. The researchers will track patients' response times and disease progression on recommended treatments.

Another hurdle Welm encountered when trying to use information from this type of research to inform patient care is the lack of insurance coverage for off-label therapies. "We have problems with drug access," Welm said. "Sometimes, we find drugs that may be FDA approved for another indication, but we cannot get it approved by insurance to be used in a breast cancer patient."

Another challenge is that the law requires that labs returning results to patients have certification through the Clinical Laboratory Improvement Amendments, which Welm's lab lacks. However, Welm pointed out that the Health Insurance Portability and Accountability Act includes a provision requiring information that can benefit patients be returned to them. In allowing lab results to be returned to patients in Welm's study, "our IRB interpreted [the] HIPAA [provision] as more important," Welm said. "They would not do that if we were going to be giving drugs that were not already approved for breast cancer."

Impact in leukemia

In another presentation at AACR, Pamela Becker, a hematologist at City of Hope, discussed a clinical trial her group conducted exploring individualized therapies for relapsed and refractory acute leukemia

based on drug sensitivity and gene expression data. Becker began the work in 2009 as a way of addressing heterogeneity in acute myeloid leukemia. Her group developed a high-throughput drug sensitivity assay conducted in 384-well plates that can test blood, bone marrow aspirate, tissue, fluids, and other samples, and began performing the assay in a CLIA-certified lab in 2015.

"We soon learned that there were over 250 recurring mutations [and] that there were distinct patterns in every individual, but there was not only heterogeneity between patients, there was clonal heterogeneity within the same patient, and there was clonal evolution over time," said Becker.

The objectives of the study were to test patients' cells in the high-throughput assay and to optimize drug combinations for therapy within 21 days, also taking into consideration mutation data obtained in the course of diagnosis. When comparing drug sensitivity results for patients, Becker said, "the most important thing to recognize is that every single patient looks different."

Out of 60 patients enrolled in the study, 35 received a regimen recommended by Becker's group. Upon following up with those patients a couple of years later, researchers found that patients who received the recommended therapy had improved survival compared to those who did not. "For patients with post-transplant relapse, they lived on average a year longer," said Becker. "One patient who received assay-guided therapy twice is still in remission four years later."

The high-throughput screen returned results in about five days. Patients were treated within eight days with overall response rates of 33 percent. Out of 22 patients with circulating peripheral blasts at the beginning of therapy, 21, or 95 percent, had a reduction in blasts. And in seven patients, or 32 percent, peripheral blasts were eradicated. Assay-guided therapy decreased risk of death by 83 percent.

In addition to the drug sensitivity screen, Becker's team looked for genomic and tumor heterogeneity insights. They used molecular data from the study to develop a machine-learning algorithm, which identified genes associated with drug sensitivity or resistance, and validated the model using 12 patient samples. They also used Mission Bio's Tapestri single-cell sequencing platform to analyze clones within the samples.

In another trial in relapsed and refractory multiple myeloma, Becker's lab screened 16 patients using a 170-drug panel, and out of 13 patients treated with assay-guided therapy, 92 percent achieved stable disease or a better outcome. "Patients who had high sensitivity to their drugs had a much longer survival than those who did not," said Becker.

Becker said the drugs used in panels for the trials included a range of FDA-approved and investigational drugs. Because of that, patients who received assay-guided therapy did not necessarily receive the optimal treatment because the choice of therapy had to be based on what payors would cover. Because of this, Becker estimated that around 80 percent of patients didn't get therapies that were ranked in the top 10 based on drug screening data.

The data from these trials on clinical features, mutations, drug sensitivity, functional screening, and clinical response will contribute to a future algorithm for optimizing precision cancer treatment strategies. "We utilize computational systems biology approaches, and future trials will be able to introduce these approaches after earlier diagnosis," Becker said. "These predictions can be tested in our future clinical trials, and then, practice … will change."

FPM in pediatric cancers

Pediatric cancers have a lower frequency of driver mutations than adult cancers, and as a result, fewer precision medicine options. Diana Azzam, a professor of environmental health sciences at Florida International University, presented the results of a pilot study carried out in collaboration with Nicklaus

Children's Hospital in Miami to determine the feasibility and efficacy of an FPM approach in patients with childhood cancers.

Investigators enrolled 25 pediatric cancer patients and generated drug sensitivity recommendations for 19 patients. The recommendations were then sent to a molecular tumor board for review, and ultimately, six patients received treatment guided by the FPM screening and seven received standard-of-care therapies.

Five out of the six patients who had FPM-guided care achieved an overall objective response, while only one out of seven patients on standard-of-care treatments had an objective response. FPM patients also had statistically improved progression-free survival compared to their previous therapy regimen. When researchers genomically profiled the same group of patients, the testing yielded therapy matches for only six patients.

In addition to providing treatment recommendations to a higher proportion of patients compared to genomic testing, Azzam said this study also showed that *ex vivo* drug testing can be performed within a clinically actionable time frame. The median turnaround time was seven days. "The results that we generated warrant a large-scale clinical trial in order to better assess and validate the implementation of functional precision medicine in childhood cancers," said Azzam.

Drug sensitivity information provided information beyond standard cancer subtyping, as well. When comparing drug sensitivity results for patients, those with the same subtype of cancer did not cluster together. Additionally, in looking at correlations between classes of therapeutics, researchers found that profiles from ethnic minority populations were distinct from other ethnic groups, Azzam said.

As a result of that finding, Azzam's team received a grant from the National Institute of Minority Health and Health Disparities, and the researchers are now enrolling 65 pediatric cancer patients in South Florida into a study to investigate whether drug sensitivity testing and FPM can reduce health disparities in children. Researchers will use machine learning to integrate functional drug testing data with results from RNA-seq and whole-exome sequencing to identify multiomic biomarkers specifically expressed in minority populations.

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