Precision Oncology Comes of Age: Tumor-Agnostic Approaches

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Colleen Lewis, MSN, ANP-BC, AOCNP®, and R. Donald Harvey, PharmD, BCOP, FCCP, FHOPA, presented on the new world of tumor-agnostic treatment approaches, including those aimed at managing patients with tumors that have high microsatellite instability (MSI-H) or neurotrophic receptor tyrosine kinase (NTRK) fusions. Learn about the clinical trial designs that enable development of these novel therapies, and discover how testing methodologies support precision medicine advances.

As clinical oncology transitions further away from classic cytotoxic chemotherapy towards precision medicine, drug development is increasingly driven by individual tumor genetics. Patients undergoing treatment with small molecules or immunotherapy, for example, are stratified by biological markers and pathways rather than simple anatomic sites of disease. At JADPRO Live, Colleen Lewis, MSN, ANP-BC, AOCNP®, and R. Donald Harvey, PharmD, BCOP, FCCP, FHOPA, of Winship Cancer Institute of Emory University discussed the benefits and drawbacks of modern clinical trial designs, evaluated testing methodologies, and assessed tumor-agnostic treatment approaches.

DRUG DEVELOPMENT

As Dr. Harvey explained, the historical model of oncology drug development has been defined by a progression of clinical trials, from phase I, first-in-human, dose-escalation trials all the way to phase III, randomized trials that pit standard-of-care treatment against investigational agents. However, oncology research is transitioning to seamless drug development or a continuous phase I trial when appropriate to accelerate promising agents. In this model of research, investigators add buckets of patients and cohorts in order to obtain deeper understanding with more rapid turnaround. A phase I trial for pembrolizumab was initiated in 2011, for example, and early activity signals led to rapid expansion cohorts and a total phase I population of 1,200 patients. Ultimately, said Dr. Harvey, more efficient enrollment led to approval in two diseases and a companion diagnostic. Nevertheless, the U.S. Food &

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Drug Administration (FDA) has safety concerns in mind.

"The FDA wants to ensure you're learning as you go for safety, so consent forms and adverse events need to be reflected in a real-time way," said Dr. Harvey. "You need to make sure that serious adverse events are provided to new patients coming on study in a real-time fashion. That can create a lot of regulatory burden, but it's still better than the classic I, II, III approach, which historically is anywhere from a 6- to 10-year timeframe." A decreased trial population has its drawbacks, however. As Dr. Harvey explained, the more efficient design of seamless trials shrinks the enrollment number, which means that very rare adverse events may not show up in trials.

"You must rely even more on post-marketing experience to get those adverse events that are rare but potentially serious," he said. "While it's certainly a good thing to get the drug to market, it can be challenging from a pharmacovigilance perspective."

Dr. Harvey also noted that dosing has become a concern with many newer agents.

"What frustrates me as a pharmacist and pharmacologist is that we're getting the dose wrong for many small molecule drugs," he said. "There are a lot of approved drugs that require a dose reduction in 80% to 90% of patients."

Finally, said Dr. Harvey, a clinical pharmacology study may be difficult to complete post approval. For example, a drug could be effective and thus accelerated through a drug-development paradigm, but the effect of food on its absorption may remain unknown. It's easier to enroll to that trial before the drug is on the market than afterwards, he explained.

PRECISION MEDICINE STRATEGIES IN ONCOLOGY

As Dr. Harvey explained, precision medicine strategies in oncology are often guided by the molecular characteristics of the patient's tumor, but there are many other ways to personalize treatment. Cancer-based approaches include tumor genomics and immune profiling at the individual and population level. Patient-based approaches, on the other hand, include individualized dosing based on pharmacogenomics, reactivity to adverse events, and therapeutic drug monitoring.

"If there's ever a place in medicine where we should be thinking about therapeutic drug monitoring, it's oncology," said Dr. Harvey, "but it just hasn't caught fire."

According to Dr. Harvey, the benefits of individualizing therapy are pretty clear: improved likelihood of depth and duration of response; prevention or mitigation of adverse events; and potential for lower doses. But there are drawbacks, as well.

"It's going to take a lot work to identify the population of interest," he said. "If you're looking for a molecular subtype of 3% of patients, that's a pretty big haystack to find a needle, particularly if it's across all solid tumors, and by definition, this approach excludes patients. There's also additional cost."

TRIAL DESIGNS FOCUSED ON PRECISION APPROACHES

As Dr. Harvey reported, there are two novel trial designs aimed at developing drugs that are truly personalized (West et al., 2017). The first protocol type is the umbrella trial, which takes patients with a single histology and then subdivides them molecularly or through other biomarkers (Figure 1). Examples of this protocol include The ASCO Targeted Agent and Profile Utilization Registry (TAPUR) trial and the Lung-MAP trial (SWOG). Next generation trials include I-PREDICT (combinations), TARGET (circulating DNA), and WINTHER (RNA sequencing and adjacent tissue profiling).

The strength of this approach, said Dr. Harvey, is that when biomarker prevalence is low, screening success rate is improved with multiple arms, and the protocol's flexible design enables investigators to easily add or drop arms. On the other hand, the large number of drugs and biomarkers can pose a challenge; the development of a multiplex assay is more complex than a single biomarker. In addition, this protocol often requires regulatory review of both drugs and assay.

The other protocol is a basket trial, which utilizes a single treatment and a single biomarker across different histologies and anatomic sites. Larotrectinib for patients with *NTRK* gene fusion is an example of this approach (Cocco, Scaltriti, & Drilon, 2018).

"Basket trials can be more efficient than multiple histology-specific enrichment trials," said Dr.

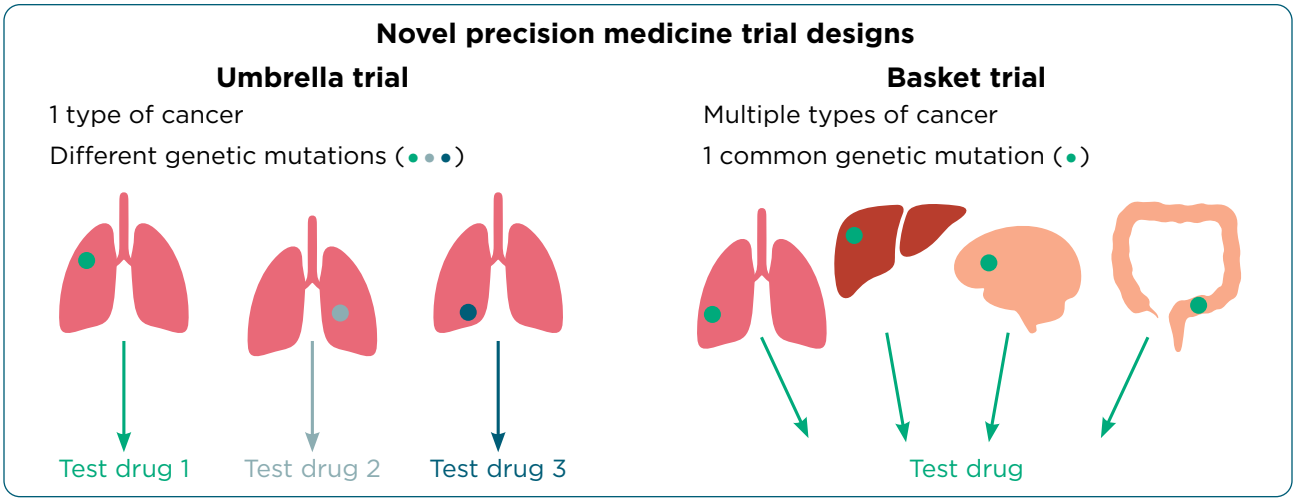

Figure 1. Trial designs focused on precision approaches. Adapted from West (2017).

Harvey. "If the treatment is already approved in another disease, investigators can quickly learn if efficacy translates to other indications, and only one assay is needed."

On the other hand, said Dr. Harvey, disease subtype is often prognostic, so the choice of endpoints is limited. In addition, without a comparative arm, investigators can't distinguish predictive from prognostic value. Finally, some baskets may have small sample sizes if a mutation is rare.

INDIVIDUAL PATIENT MANAGEMENT STRATEGIES

As Ms. Lewis explained, incorporating precision oncology into the management of individual patients requires clinically meaningful information about their disease in order to make relevant therapeutic decisions. One common way to obtain that information is through next-generation sequencing.

"It's interesting that approximately 80% of oncologists have indicated they are using and ordering this information, but half have challenges interpreting the results," said Ms. Lewis. "I think we can all relate to that: Sometimes we get the report back and are left with more questions than answers."

Figure 2 shows the use of next-generation sequencing tests over the past 12 months among oncologists in the United States (Freedman et al., 2018).

TISSUE TESTING

Tissue testing is one of the major factors to consider when ordering next-generation sequencing, said Ms. Lewis. The current gold standard allows for histologic interpretation and non-DNA–based alterations (hormone receptors). However, due to tumor heterogeneity, a biopsy may capture only a partial genomic landscape of a patient's disease, which can misguide interpretation and treatment decisions (Miles et al., 2015). In addition, radiation and DNA-damaging agents can impact the genomic heterogeneity of recurrent/metastatic disease. In patients who have received these agents, said Ms. Lewis, clinicians may need to repeat a biopsy. Patients may also require multiple samples over time to assess evolving changes, and high-quality specimens are required for best information. The abundance of circulating tumor DNA also increases over time, said Ms. Lewis, so liquid biopsies could be useful to detect those alterations (Corcoran & Chabner, 2018).

WHEN TO ORDER NEXT-GENERATION SEQUENCING?

As Ms. Lewis reported, the age of archival surgical tissue is another factor to consider when ordering next-generation sequencing. The literature recommends that tissue be no older than 5 to 7 years. The older the sample, said Ms. Lewis, the more challenging it is to extract DNA and obtain meaningful information. For patients post-neoadjuvant therapy, unresectable, or newly metastatic, an extra core specimen is require for next-generation sequencing. Clinicians should also consider ordering this test earlier for patients at high risk

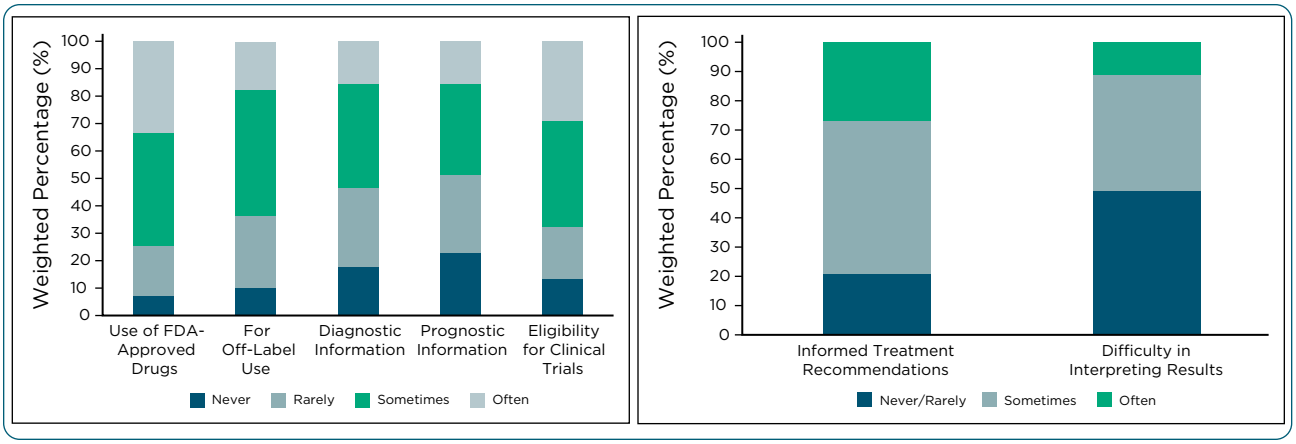

Figure 2. Clinical use of next-generation sequencing: current landscape. (A) Use of NGS tests by clinical purpose over the past 12 months among oncologists in the United States. (B) Use of NGS testing over the past 12 months among oncologists in the United States. Adapted from Freedman et al. (2018).

for recurrence, said Ms. Lewis, because it can take a long time to get the results back.

Finally, there are insurance considerations. In 2018, Medicare released a decision memo regarding coverage for next-generation sequencing. Testing is currently covered for recurrent, metastatic, relapsed, refractory, or stage III or IV cancer. Repeat testing is covered for the same next-generation sequencing test only for a new primary cancer diagnosis and for a patient who has decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

INTERPRETATION OF RESULTS

According to Ms. Lewis, it's imperative to educate patients up front so that they have some degree of expectation. There may be a scenario where there are no actionable mutations or there may be a mutation that helps select therapy or is associated with resistance to molecular therapies. There could even be multiple actionable mutations, said Ms. Lewis, so it's important to explain the difference between driver and passenger mutations. There may also be challenges posed by discordance with blood-based circulating tumor DNA and other platforms (Nagahashi et al., 2019).

"If patients have had multiple platforms done, you might see some different results on those tests because of the difference in depth of reads," Ms. Lewis explained.

"We're seeing evolution in this space of tumor-agnostic approaches, and it will continue to get more challenging, but hopefully we'll also develop more effective therapeutics over time," Dr. Harvey concluded. "You can see deep responses in these populations. The biggest challenge is resistance development, but hopefully that's offset by an improved tolerability profile of drugs. We can inform decisions, but there are limitations with the platform of testing. Trials are always important to understand how we can apply this technology." ●

Disclosure

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