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INTERVIEW

Genomic Testing: New Frontier in Cancer Therapy

 Axel Grothey MD (/Profile/7)  Lee S. Schwartzberg MD, FACP (/Profile/5)

Dr. Lee Schwartzberg and Dr. Axel Grothey discuss the current status of genomic profiling and its potential to change therapeutic strategies in oncology.

Dr. Schwartzberg: Dr. Grothey, do you order FoundationOne™ testing, or other genomic testing?

Dr. Grothey: Yes, and I do so more and more frequently these days. There are many more targeted agents available today that can block certain pathways. For a long time, we have been moving away from an organ-based classification of disease and toward a more pathway-based classification. We are at a transition point right now, where we utilize certain agents and classify tumor types more on a biologic basis than on an organ basis.

The availability of these agents, plus the availability of gene-based tests, makes this approach attractive. The question now is whether this will translate into benefit for the patient. I think this is still an open question.

When to use genomic testing

Dr. Schwartzberg: I have devised an algorithm for the use of gene-based tests that yield mutational analyses. I use those tests for tumors for which there is no standard of care or for which we have exhausted the standard of care. For example, for a patient with a biliary tract cancer, standard first-line therapy is a platinum agent and gemcitabine. There is no standard care after that. In that case, I would obtain a gene panel. In breast cancer, where there may be several standard therapies beyond first-, second-, or third-line, I might delay getting a gene panel for a much longer period of time.

The gene panels that Dr. Grothey and I are referring to are not necessarily the ones that are directly actionable. That is, we are not referring to getting ALK or EGFR testing for a patient with lung cancer, which is recognized by every guideline group as standard of care for every patient. The panels we are talking about are the ones that now include 50 genes or 104 genes, or even 405 genes, and they analyze a variety of genomic alterations in all of those genes. We try to determine whether there is an alteration that could potentially be actionable with regard to a clinical trial or a drug that's already available.

Actionability

Dr. Grothey: It's a lot like a fishing expedition, initially, when you don't know what you'll find. Then, when you have found something, you don't know whether the intervention you might have in mind, when there is a drug available, will actually work for this particular alteration. We still lack understanding. The question we face is always, "What do we do with the information?" The easy way out would be to enroll the patient in a clinical trial specifically designed for patients with a specific mutation. But clinical trials are not always available for every patient who has this need.

On the other hand, you might be considering off-label use of a certain agent or combination of agents. Then you start negotiating with insurance companies. These potentially available agents are not cheap, and you are using them off-label.

Finally, there is the issue of whether you need to re-biopsy the tumors. For later lines of therapy, you may be running out of treatment options. Do you need to re-biopsy certain areas of concern? Which metastases do you biopsy? The rationale for a repeat biopsy is that, over time, the tumor might have changed its genetic profile.

Dr. Schwartzberg: You have brought up some very important points.

In truth, there's really not a lot of actionability related to these genetic panels, particularly when we see a gene mutation. We are still in the very early stages of our use of this testing. Even in centers such as ours, where there are large clinical trial options for patients, there is not a lot of actionability. This is true even across the universe of clinical trials: there may not be a good fit for these patients.

It is very important, as with other aspects of oncology, to have a discussion with the patient and to set his or her expectations appropriately for what this testing is and what it is not. The patient needs to be properly apprised of the potential benefit and lack of benefit from doing one of these tests.

Understanding the context

With regard to the significance of the pathway information, we don't understand the entire context yet. For example, a BRAF mutation in colon cancer means something very different in terms of response to a BRAF inhibitor than it does in melanoma. The interactions with driver-mutation oncogenes are contextual and are, importantly, different among different diseases. There are definitely differing diseases in which a specific mutation has similar consequences, despite varying tissue of origin. Conversely, there are diseases in which the same mutation may lead to different interactions, as a consequence of differences in the originating organ.

Tumor heterogeneity

One very critical issue is tumor heterogeneity. Currently, we do not have enough evidence to guide us on how to address this issue in clinical practice. Should we take multiple biopsies of the same tumor? Should we take biopsies of multiple sites in a patient, to see if there are different driver mutations? Our understanding at this point is rudimentary.[1,2,3,4,5]

In using traditional chemotherapy, we very rarely see mixed responses in most solid tumors. The patients respond or not, which assumes that, whatever the target was for traditional chemotherapy, it was maintained in all sites. Anecdotally, I see somewhat more heterogeneity of response when I use targeted therapy. This does not occur in every patient, and, therefore, it does not necessarily translate to a clinical impact, even with different mutations.

Treating patients despite limited knowledge

Dr. Grothey: The theoretical discussions and the preclinical concerns about tumor heterogeneity are important, but we also need to treat patients. At some point, we need to bite the bullet and start treating. Eventually, we try to change patients and our models. Sometimes it really works. Lung cancer is an amazing example. In spite of the fact that there may be, and likely will be, tumor heterogeneity, this fusion protein is

apparently driving the biology across the human body, across various disease sites.

I would like to know whether the perception—the perception that there is a greater occurrence of mixed response with biologic agents than with chemotherapy—is real.

Dr. Schwartzberg: The point you have is an excellent one—eventually we have to make a decision to treat the patient based on the information we have. We take the information available and try to integrate it.

Dr. Grothey: Genetic profiling is likely going to be the wave of the future, maybe not for every patient in the next 2 to 5 years, but we are moving in this direction. Our challenge is to validate the tests and our use of them—to show that this approach is better than the empirical approach we've used thus far.

National registries and clinical trials

Dr. Schwartzberg: It would be great to see clinical trials that prospectively randomized patients to empirical therapy or treatment of physicians' choice vs molecularly derived therapy, based on the genomic profile. I hope those trials get done.

Dr. Grothey: I would like to see a national registry established to track how clinicians act on the information they obtain from genetic profiling. A lot of tests are being used right now, but we have very limited information about the consequences. For example, how many patients will have actionable mutations? How many patients will go into clinical trials? How many patients will be treated with an off-label use of a certain agent, and with what outcome? Answers to these questions could serve as benchmarking data in designing clinical trials.

References

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