Overview of Precision Medicine: Past, Present and Future

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Dr. O'Dwyer provided an overview of precision medicine, beginning with definitions in the field and descriptions of various genomic tests. He then discussed molecularly guided trials, including study design issues and specifics of ongoing studies.

The goal of precision medicine is to deliver the right treatment at the right dose to the right patient at the right time. There is concern over the promise versus the reality of this goal, particularly in the clinical trial setting when physicians meet with individual patients trying to decide whether to enter the study. The promise versus reality must be presented realistically, and both parties need to be informed.

When considering molecular testing methods, it is important to ask several questions, such as whether the technology is robust and reliable, whether it can find actionable mutations, and whether patients are likely to benefit. Currently, molecular testing is not standard of care for most tumors, but is instead an option. For most cancers and mutations, the benefits of molecular testing have not been quantified, despite the success of selected individual cases.

Tumors evolve, particularly in the presence of treatment. Biopsies from different regions of the primary tumor can show different mutation profiles, as can biopsies from metastatic tumors. Biopsies from circulating tumor DNA might give a better representation of the heterogeneity of tumor than single biopsy, so these noninvasive liquid biopsies are likely to be incorporated into future precision medicine trials.

Genomics should be considered in the context of tumor biology, which is influenced by many factors. Different types of therapies are being developed for the many possible targets in cancer besides mutations in the genome. These include treatments designed to influence epigenetics, the immune system, and the tumor microenvironment, in addition to stem cell-informed therapy.

Current precision medicine trials have established the feasibility of a molecularly guided approach, although it is too early to judge its benefits. Nevertheless a molecularly guided approach to cancer treatment is superior to "flying blind" and hoping for the best. Trials targeted to specific patients seem most likely to advance curability of cancer, and this may eventually include multiple treatments that target different aspects of tumor biology.

<u>Audience Questions and Answers</u>

- *What expectations should patients have regarding side effects of precision medicine therapies? Shouldn't a by-product of molecular targeting be minimal side effects?* If we had drugs that were targeted only to the aberrant proteins, they might be associated with minimal side effects. Today's medications also bind to the normal protein, which can cause side effects. It is also important to note that molecularly guided therapies may be differentially effective at different times in the

course of cancer, and patients may be more or less likely to accept side effects depending on where they are in the course of their disease and the probability of cure.

- *If tumors are heterogeneous, is there a danger that biopsies could lead us to a wrong target?* Yes, that is a real concern. That risk varies depending on whether the aberration is present in both the primary tumor and the metastasis. If the mutation is present in both, tumor biopsies would be likely to detect it. If, however, there is an additional mutation in the metastasis that might have a bearing on response to therapy, sampling the primary tumor may miss it, but liquid biopsies may detect it.
- *In several examples of clinical trials, you said that the drug wasn't available, but how did that happen? Why are we accruing patients to that trial if the drug is not available?* There are various reasons for this; for example, the drug may not be available for a given population or may be withdrawn from the market. This is a developing area and is a consideration when incorporating the latest science into trials.
- *You didn't mention sequencing for microsatellite instability-high (MSI-high), which means a lot of mutations in the tumors, and pembrolizumab is approved for any cancer that is MSI high, which seems like standard of care.* Yes. Historically, we've identified that by immunohistochemistry because if the protein is missing, that information is as useful as sequencing. Answer by Stanley Hamilton, MD: The current problem is that no clear biomarker is available to identify patients with high mutation burdens, and that's what is really involved with MSI. That, along with several other key mutations, lead to high rates of mutations throughout the genome. The end result is neo (new) antigens from different protein products that result from all those mutations that lead to response to checkpoint inhibitors. The problem is that there are now 7 or 8 different assays that pick this up; MSI was easiest to do because it's been around a long time and the techniques are well established. The problem now is what to do on a broader scale, particularly because if you look at mutation burden diagram, there is overlap between the number of mutations in the most mutated tumors and the ones at the low end. Only tumors on the upper end of the curve respond even though the mutations are present in lower load tumors. There are not established cut points for mutation burden or mutation load, and this may be different in different tumors. Much laboratory work remains to be done.
- *Because we don't have sequencing standards, results from different sequencing providers may be different. Doctors may not be well trained to deal with this issue.* This question may be addressed in Stan's talk. Different assays may give different results, but it doesn't mean they are wrong. When physicians get the sequencing reports, they have no way of interpreting the strength or weakness of that association.
- *When discussing the definition of precision medicine, we are saying that immunotherapy doesn't fit the definition. Yet some of the best progress seems to be a combination of pathway inhibition plus immunotherapy, so these paths are crossing. Are we going down a road that will inhibit people's understanding by dividing precision medicine from immunotherapy and do we need to consider different terminology? We are probably in a position now to influence these definitions.* First, conceptually, the term targeted therapy indicates that the treatment is targeted toward particular molecular abnormalities . Conceptually, this is a useful way to think because they are different. It makes it clear how you are thinking about a treatment and its effect, which is useful. But the limitation I agree with, that we shouldn't ignore immunotherapies in future iterations of these studies. The combined administration of targeted therapies and immunotherapies is in its early

stages. There is little data to support that this is a widespread phenomenon. Preclinical data suggests that it will be useful, but we don't know enough about it to declare that this is the only way forward. It is definitely a way that has to be explored. In the next iteration of the MATCH trial, these combinations are going to be really important.

- *We talk about sample size and gender in trials, but we don't talk about race. There is a problem getting people of color into clinical trials. When they are in clinical trials, it's important to include those numbers so that we know all patients are being helped by the drug. How do you think we should do that?* We are doing this in the MATCH trial. We have about 9% African American, but the population that is under-represented is Hispanic ethnicity. Currently it's about 4-5%, but it should be around 10-11%. So, the representation of minorities in MATCH trial is not quite as high as it should be, but it's close. The bigger question that you raise is, when you get the results, even if you do have significant minorities in the whole population, will you know that an African American patient is as likely as the majority population patient to respond or not get toxicity? That part is a numbers issue. You'll see that each of the subgroups in the MATCH group is a phase 2 study and it only comprises 35 patients in the first stage—some went up to 70. But if you take 10% of 70 patients, that's only 7 patients. Statistically speaking, the likelihood of finding meaningful interpretation in a study like that is not very likely unless you have a huge signal. Usually those questions need to await larger trials. The approach that we are taking in ECOG ACRIN is a scientific one: race is a variable, and we want to know how that and other variables influence clinical response to treatment. We are trying to define how to do that.
- *There has been recent refinement of diagnosis in clear cell kidney cancer according to gene expressions or cluster analysis. Among these subgroups is one that has the poorest outcomes, and African Americans are overrepresented in this group. Even before precision medicine, this would suggest that African Americans might be tested for this gene expression group that would instantly change treatment and/or monitoring. How does this kind of knowledge fit into precision medicine?* The clarification of that fact in kidney cancer came from large trials in which patients were genomically tested, and that subgroup of patients with the inflammatory type of tumor is clearly different from rest of the clear cell population. Probably the biggest determinant we can identify is that it is more common in African American patients, but there are many African Americans with kidney cancer who don't fit into that subgroup. Thus, we need to understand race as a variable that is important in defining therapy.
- *Are the agents being tested in precision medicine trials under INDs or are they FDA approved?* In the TAPUR trial, all medications were approved for other indications. In MATCH, several agents are under INDs, but not all. Clarification from audience member: If you are using a drug off indication in a trial, it still requires an IND.
- *Would data from genomic trials be different in societies such as France that are not as heterogeneous as ours?* **I**t appears so. I think that there is insufficient breakdown by race of particular genomic abnormalities across a whole span of tumors. If you take colorectal cancer as an example, there isn't a lot of variability based on race. The key abnormalities driving these tumors are found across all groups of patients with colorectal cancer. But there is certainly room to analyze this further because we know, for example, at some stages of certain tumors, some groups do worse, such as African Americans. There is likely to be a genomic contribution to that. There are likely some genomic differences, but they haven't been found yet. Answer by Stanley Hamilton: The most glaring example we've found of this is MSI. You almost never see this in Hispanics unless they

have the inherited Lynch syndrome. This is a clear observation that this ethnic group doesn't get MSI high tumors.

- *Other researchers have described differences between blacks and whites in colorectal cancer and between men and women. This seems to contradict what you are saying.* I may not be aware of all of the literature. They may have data that I've not yet seen.
- *In MATCH, 10% of all screened patients had actionable mutations, but in earlier studies it was 40%. Why this difference?* The difference is in how you count an actionable mutation. In the older trial, they counted mutations for which they didn't have a targeted treatment. Actionable is not a scientific term. It depends on how tumors were characterized (breadth of platform) and what abnormalities had treatments available. The availability of drugs was highly variable across studies. In MATCH, the "actionable" mutations excluded those that were known and for which there were currently available drugs. The final actionable rate in MATCH was 19%. The aberration rate is much higher, but we didn't have treatments for all of those mutations.
- *Is there a strong generational genetic component to colorectal cancer and are there studies that have looked at this?* Yes. The risk of colorectal cancer for any of us is 5%. If you have a first degree relative with colorectal cancer, the risk rises to 10%. This impacts the frequency of recommended screening and the age at which screening starts. For families with high rates of colorectal cancer, we recommend very early screening because it is curable if you get it early.