Transcript Details
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Exploring the Clinical Value of IGHV & TP53 Sequencing for CLL

Announcer:
You're listening to *Project Oncology* on ReachMD, sponsored by Lilly. Here's Dr. John Byrd.

Dr. Byrd:
The prognostic relevance of IgVH mutation and P53 mutation or deletion are probably one of the most predictive for how CLL is going to behave at diagnosis with respect to time, to progression, and in the past overall survival, as well. The variability between these two when you look at them along with all of the older prognostic factors that we use clinically, and with routine labs such as the CBC parameters the hazard ratio for contribution of P53 mutation or deletion is probably the greatest but only a small subset of CLL patients have this at diagnosis, so it's not as helpful, 5 to 10 percent, whereas the IgVH mutation if one is unmutated, that's gonna correspond to approximately 40 percent of patients at diagnosis how are gonna have a relatively rapid progression to time of treatment in the past with older therapy, shorter survival. Whereas 60 percent of patients with IgVH mutated disease will often have a very extended natural history before needing treatment; some never requiring treatment and a prolonged survival.

A common question that providers often ask is what type of prognostic information to test like the IgVH mutation test and P53 mutation or deletion bring to the table as we're seeing patients initially. Prognostic factors are exactly that, they're something that are used at different time points within the disease to predict how a patient's disease is going to behave. In CLL, when we're seeing patients initially, we use prognostic factors to predict two things; how long the patient is gonna go from being asymptomatic to being symptomatic and requiring treatment and how long the patient is gonna survive with the disease. The P53 mutation or deletion when present in CLL has a very strong predictive value of saying a patient with CLL is going to do poorly, is going to progress quickly, and is often going in the past with our older therapies, is going to die quickly from their disease.

The international prognostic index looks at many different things relative to biomarkers in the past and the present that you know, that impact CLL outcome. And from a large group of European and U.S. patients was able to decipher the contributing role, an independent contributing role of certain features. At the top of that, in terms of providing a high score, which corresponds to the hazard ratio of bad outcome, P53 either mutation or deletion falls, IgVH mutational status is also a a contributing factor it's assigned a lower it's a sign of lower scale or score than P53. But together, these two are driving features with some of the clinical features used in this. This score was designed both for trying to predict who is going, at diagnosis, is gonna have a high chance of progressing to requiring therapy and have a short overall survival with chemoimmunotherapy.

The applicability of this to predicting outcome time from diagnosis to treatment has persisted with the introduction of the targeted therapies. Either you know the BTK inhibits, like acalabrutinib or venetoclax. However, when looking at survival because these therapies are to some extent agnostic of IgVH mutational status and P53 mutation, you see less of an effect of this in predicting how people are gonna do with therapy. But, it still provides an index to compare at cross trials where you normalize patients based upon a relative risk of each factor and this makes this tool extremely useful when looking at data with different treatments from different parts of the world where the time you initiate treatment might be different.

So, clinicians when they're looking at a patient who's symptomatic and needs treatment for their CLL has to call into question several variables as to making that decision. Clearly one is the age of the patient and the functional status of the patient. When you get outside of that, though, you know the laboratory tests that are most helpful when you're sitting in front of a patient in terms of deciding therapy, initially therapy for CLL, the question becomes, "Well, what's useful?" And probably the two most useful tasks are the IgVH mutational status and the presence or absence of P53 mutation and/or deletion. They're different but they correspond to relatively the same thing relative to predicting outcomes. The IgVH mutational test and knowing its status before starting therapy, particularly in a young person is

important because patients with CLL who are IgVH mutated have the potential to be cured with fludarabine, cyclophosphamide, and rituximab.

The P53 mutation or deletion comes down for another reason. Almost all patients who have P53 mutation or deletion have IgVH unmutated disease. So, we would be directing them toward a targeted therapy. And when we approach targeted therapy in CLL, this is the P53 status is important because right at the present time, there's really only one study that has looked at the venetoclax-based treatment for in 17P patients and this study showed that the 17P P53 mutated patient who received venetoclax plus obinutuzumab for twelve months had a very short progression-free survival relative to other studies that use BTK inhibitors. The BTK inhibitors, either by themselves or with obinutuzumab, when I say the BTK inhibitors, I'm referring to acalabrutinib and ibrutinib they had longer progression-free survival, albeit with continuous therapy of the BTK inhibitor say than venetoclax. So most CLL thought leaders if we're their 17P patients, until there's more data with combinations as part of clinical trials would assign this patient group to a BTK inhibitor either by itself or with a CD20 antibody or as part of a trial combination with something else.

Announcer:
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