What is the significance of IGHV mutations and how are they assessed?

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TRANSCRIPT & FIGURES

Now we are going to talk about whether there's still a role for chemotherapy or chemoimmunotherapy in the treatment of CLL, now in the era of novel kinase inhibitors. This is a very important topic because we have some new recent exciting data on the potential benefits of chemotherapy. As you know, the standard chemoimmunotherapy treatment now for fit younger CLL patients is something called FCR (fludarabine, cyclophosphamide and rituximab) and this is a treatment given infusionally by vein for three days, every four weeks, for about six months. This treatment has been studied in multiple large trials and we now have long follow up from three of them that report specifically on a genetic subgroup of CLL, a subgroup of something called mutated IGHV, which I'll explain more in a minute. These three trials all report that people with mutated IGHV CLL can have extremely long duration of remission after FCR treatment. In fact, at twelve years, about 60% of such people are still in remission and likely many of them are cured, many of them have no evidence of disease by the most sensitive tests.

So, what does it mean to have mutated IGHV? The IGHV test is something that we do on the CLL cells. CLL cells come from a normal cell called a B-lymphocyte, and B-lymphocytes have an antibody gene in them. The antibody gene can get changed over the course of the life cycle of the B-lymphocyte. All CLL cells have the same one and it turns out that how much the antibody gene has changed from the day you were born has a very strong impact on the way CLL behaves. So, a so-called mutated IGHV shows much greater change from the way it was when you were born in the antibody gene. This has

been found empirically to associate with better behaving CLL, longer time to treatment and better response to treatment, and now with these FCR studies, perhaps even cure with FCR.

The other subgroup of CLL, the unmutated group, has an antibody gene in their CLL cells that looks much more similar to how the gene was when you were born which is why it's called unmutated. It is associated with more steadily progressive disease and after FCR; we see more steady relapse although the median duration remission is still on the order of about four to five years.