ASH 2017: Dr. Constantine Tam on the Prognostic Value of IVGH mutation status in CLL - Transcription

Dr. Brian Koffman – Hi. Dr. Brian Koffman, founder and medical director of the CLL Society here at ASH 2017.

Dr. Constantine Tam – Hi. I'm Dr. Tam from Peter MacCallum Cancer Center at St. Vincent's Hospital in Melbourne, Australia.

BK – So, one of the things that patients want to know is, “Am I a high-risk patient? A low risk patient?” And there's a lot of risk/prognostic factors that look at that and one is IgVH. Can you explain what that is and why that's important and maybe some new research that you've been involved in… that it may not be as black and white as we thought before.

CT – Sure thing. IgVH. So, we need to just take a step back and think about what the normal immune cells do. So, CLL emerges from a normal immune B-cell. The normal immune cells are born with a receptor that allows it to look at germs and things that it runs across

BK – And cancer cells.

CT – And cancer cells, for that matter! And each immune cell has a unique receptor which allows it to identify and recognize a particular germ or cancer. Now there's a process called “mutation” which means that if you're born with a certain receptor and it fits a germ pretty well, but not 100% perfect, then the normal immune cell mutates that receptor and changes in subtle ways until it fits really well. And then that cell becomes the cell that makes you immune to that germ in the future.

BK – That's a more mature cell than the unmutated cell.

CT – Correct. So, an “unmutated” cell is born with a very generic type of receptor. A mutated cell is one where the receptor has been mutated to fit the germ or the target very well. So, an IgVH mutation tells us how mature a certain cell is. Now, this is in a normal setting. If you take cancer, which emerges from our immune cells in the first place. In general, in cancer, the more mature you are, the more likely the better you do.

BK – The less aggressive the cancer tends to be.

CT – Precisely, the less aggressive it tends to be and the better it responds to treatment. In the case of chronic lymphocytic leukemia, we know that your IgVH mutation status is very important. In particular, if your receptor is not very mutated at all, or unmutated, it means that the cancer emerged from a younger, less mature B-cell and it tends to be more aggressive and responds less well to treatment. If you are IgVH mutated, it means that you've got a more mature receptor. The cancer emerged from a more mature B-cell. You tend to do better. And this is one of those situations where people often grapple with the terminology, because in cancer medicine when you hear the word “mutated”, you obviously think “bad”. But in this case, “mutated” is actually good. Now, this is actually really important for patients with chronic

lymphocytic leukemia, because in recent years we've realized that some patients may be cured by chemotherapy with FCR chemotherapy. and I know that when I went to medical school and even about five or ten years ago, we were telling people that CLL is not curable. But now that we've actually got more long-term results from FCR chemotherapy, we realize that some patients do not relapse. And the people who are cured or who have the potential to be cured are the ones with the mutated IgVH receptor. So, this is the more mature CLL.

BK – So, as a patient, if you're going to be considering chemo-immunotherapy, it would make good sense to know what your mutation status was before you make a diagnostic… a treatment decision, I should say.

CT – Absolutely. So I would say for myself in a world where a lot of people are moving away from chemotherapy, that was targeted therapy ,that a crucial decision for me would be to know what the IgVH mutation status is because if a patient has an IgVH mutation status that tells me that there is not a bad chance of cure with chemotherapy, even in the scenario where they can get a non-chemotherapy treatment. It may still be a good option for that patient to get chemotherapy with the risks and long-term side effects of chemotherapy, because there is a real chance that they may never need to be treated again. Now there is some new information to emerge in this Congress. Traditionally, right from the start, we have defined mutated versus unmutated on a 2% threshold. So we'll say, if your receptor is less than 2% different from the way you were born, you are "unmutated". If your receptor is more than 2% from the way you were born, then you are "mutated". Now that 2% threshold turns out to be… it was drawn out of the air and decided somewhat arbitrarily many, many years ago and it's followed through in all these subsequent studies. So, what we did in the MD Anderson group and led by Dr.? and Dr. Keating, was to answer the question, "Well, is that true? Does a 2% threshold really hold up? If you are 2.1%, are you different from 1.9%?" So, what they did was they got all the patients treated with FCR at MD Anderson, and instead of classifying them as "unmutated" and "mutated", they actually divided them into percentages of mutations. So instead of saying less than 2% or more than 1%... more than 2%, saying one, two, three, four, five, six, seven, eight, nine, 10% and they actually asked how the individual patients do with the different mutation thresholds…

BK – Okay.

CT – … and was 2% the right cut point to choose? What they found, and what we find was, surprisingly, was that in fact there is no good cut point. So, 1 is better than 2, but 2 is better than 3, and 4, 5, 6, 7, 8, all the way down to ten. So, there's actually a spread of spectrum where 10 is the very best and 0 is the very worst, but there is no good spectrum in between where you might say, his is where we should say well, this is where we should draw the line. So potentially, that is very important because it redefines the way we think about mutation status. I suspect that until more data emerge from other hospitals and centers showing the same results, traditionally, by tradition, we'll still stick to the same 2% cut point, but it is very intriguing data to suggest that we should look further.

BK – That's really interesting data and it makes sense, you know, in terms of everything else we do in medicine. If your blood sugar is at one level, you're diabetic, but if it's one point less, you're not. But they both need treatment. So, if your cholesterol is here or there, you know, these arbitrary decisions are man-made, not nature made.

CT – Indeed. Indeed.

BK – Yeah.

BK – Any final thoughts on the mutation status that you wanted to share with patients?

CT – None, except I think at the moment it's an important test to be done. In my view, if they either choose two tests for CLL, it will be assessment of the p53, which… actually it will be three tests… but the assessment of the p53 by sequencing and by FISH, and IgVH mutation status. I think those are the most important tests.

BK – Dr. Tam, thank you so much for moving the science forward and helping patients. Thank you.

CT – You're welcome. Thank you so much.