ASH 2017 - Dr. Kostas Stamatopoulos on Stereotypic Immunoglobulins in CLL - Transcription

Dr. Brian Koffman – Hi. I'm Dr. Brian Koffman, a family doctor and a CLL patient myself, here at the very last minutes of ASH 2017 in Atlanta, Georgia, representing the CLL Society.

Dr. Kostas Stamatopoulos – Hi. I'm Kostas Stamatopoulos. I'm a hematologist working in Thessaloniki, Greece. I'm a member of the Board of the European Research Initiative on CLL.

BK – ERIC?

KS – ERIC.

BK – There's a lot of interesting basic science in terms of understanding how there's different families of CLL, and how it progresses, and different prognostics. And one of the things that we look at is this heavy chain and whether it's mutated or unmutated. But you've done much deeper research on that. Help me and a patient understand what's going on there. If you can just start at the very basics of why we look at that and how it helps differentiate the different risks in CLL.

KS – So, Brian, CLL is a unique malignancy in that, like other B-cell lymphomas, it originates from a mature B-cell. Mature B-cells express immunoglobulins, and they communicate with the environment through these immunoglobulins. They receive signals, and these signals, for some types of immunoglobulins, may lead to activation of the cells. Activation means proliferation and this leads to quite a few bad things in CLL. Now, it all started about 20 years ago when Nicholas Chiorazzi and Freda Stevenson showed that you could discriminate patients… you could subdivide patients… into two categories, with mutated or unmutated immunoglobulin genes. I will not delve much into the biology because it's rather complicated. The bottom line is that, in terms of prognosis and outcome, that patients with mutated immunoglobulin genes experience, in general, a far more indolent disease course, compared to those…

BK – Slow growing.

KS – Yes. Whereas the unmutated ones have a more aggressive disease, again, on average. They're enriched for adverse biological features, so they are more aggressive. It's a more aggressive form of the disease. This was a landmark in the history of lymphoma biology, at large… cellular and lymphoma biology, at large. And it was a landmark because immunoglobulins are normal things. They are expressed on normal lymphocytes. They are expressed on malignant lymphocytes. So, they are not, per se, a gene… an aberration, which makes them another unique kind of bio-marker. When these papers came out, it was, as I said, 20 years ago. There was much enthusiasm because these papers linked fundamental immunological research with patient outcome, and it was indeed a paradigm shift. Traditionally we think of cancer as a genetic disease, but now it appeared that, at least this cancer, was an immunological disease. So, we went on and studied immunoglobulin genes in different patients and over the years we collected many, many, many sicknesses… from different patients… many sicknesses from immunoglobulin genes, in different patients. So, each tumor is a clone of cells.

Each CLL is a different clone. Now, please, let's forget for a minute, CLL. Lymphocytes… B-lymphocytes… there are many millions of them… billions of them in our body. And each of them is unique, and it becomes unique due to expressing a unique immunoglobulin gene. So, every B-lymphocyte and its progeny will express the same immunoglobulin that is encoded by the same immunoglobulin gene, which makes this gene a unique identity for that lymphocyte and its progeny… in other words, for the B-cell clone. Now, let's move from one individual, from the normal setting, to CLL. And let's consider every case of CLL as a unique clone of B-cells. Now, you remember I said a minute ago that each of the billions of different B-cells, B-cell clones, expresses a unique immunoglobulin, and if this were a random phenomenon, you would need to study billions of different clones to find two with identical immunoglobulins. About 15 years ago, we realized to our utter astonishment, that we had some hundreds of cases… some hundreds of different clones, and by studying the immunoglobulin genes we could find some different patients where the immunoglobulins were identical… already highly similar. As you understand, this was a major surprise because it went completely against what we'd learned in immunology… that the immune system strives for diversity. By extension, it implied something else, as well. When you have one patient here in the U.S., and another one in Greece, and a third one in Sweden, and the fourth one in China, expressing the same immunoglobulin, this means that sometime in their life, the B-cell expressing that particular immunoglobulin, was selected by an antigen… was selected by something… which gave rise to this expansion that we call CLL. So, it was a long answer but now I'm coming to the point. “Stereotyped receptors” is the term that we use to describe the existence of immunoglobulin receptors. They are receptors for antigens… immunoglobulin receptors that are highly similar. Stereotype is a Greek word, it means to be repeated without variation. So, these repeated structures can define groups of patients…. patients sharing the same, or highly… Sorry, my mic came out… so patients sharing the same or highly similar immunoglobulin are classified into subgroups. We call them “stereotype subsets”. And work by many groups, including ours, has provided information, and is providing information almost by the year, that these stereotype subsets, may in fact, prove to be distinct variants of the disease… with distinct biological background and more importantly I guess, for every patient, but also for every physician. It appears that some of these stereotypes, may have a distinct…

BK – I apologize… (Cell phone rings). Go ahead. Sorry.

KS – So, some of these stereotypes may have a distinct prognosis and distinct response to treatment. Let me make it more clear. Suppose that you're focusing on unmutated CLL. It's expected to be uniformly aggressive, on average. Now within this great category, we have different subsets, each defined by a unique configuration of the immunoglobulin, and they can differ in prognosis from quite good to very, very aggressive. But even more important, let's go now to the other group, mutated immunoglobulin genes. So, this category of patients who are expected to follow an indolent clinical course, and yet within this broad category, we can identify some subsets that deviate a lot, and have an outcome that is very aggressive. So, having this

information appears to be informative for better understanding the biology, but also in the end, considering alternative treatments for some of these patients.

BK – And you presented some research on this. Is that something that might be accessible for patients to understand in terms of…

KS – Absolutely yes. Absolutely yes. We're showing that some of these subsets, as I told you, have different clinical outcomes and those are different responses to various treatment modalities. So, it appears, for instance, at least in our ex vivo experiments, because this is still pre-clinical, that there are differential responses of some of these subsets to the novel agents. The bottom line is that in the new ERIC recommendations that were published earlier this year in leukemia, we recommend to diagnostic labs offering this service, to include beyond the report on the somatic hypermutation status, mutated or unmutated… to use a bio tool that is free… a bioinformatics tool that is free… that we developed, and that ERIC is offering free to the community for checking if the immunoglobulins of that particular patient might belong to one of the well characterized stereotyped subsets with a distinct prognosis. Because if it's subset two, for instance… a group that we call “subset two”. Although the immunoglobulin genes are mutated, the prognosis is, unfortunately, bad.

BK – So as a patient, if I wanted to access this in the U.S., would I have to send you the lab reports from my mutation studies, or would I have to send you actual blood? Or what would I have to do to do this?

KS – There are different possibilities. First of all, U.S. labs offering this service, this test, should be utilizing the tools that are available for thorough analysis, and more particularly, thorough interpretation of the results. So, what they can do, in order to provide you a complete service and a complete test, they should employ the tool, and they're very, very welcome to contact us. ERIC has two established networks for biomarker profiling. One is about TP53 analysis. The other is about immunoglobulin genes. And I'm supervising the activities of the network on immunoglobulin genes. And in particularly, together with Fred Davi from Paris, we supervise the certification of labs performing the test. I'm glad that U.S. labs have started to apply for certification. So, what the patients should or could ask… I shouldn't say “should”, but “could” ask is, "Are you certified by ERIC for providing accurate results, and particularly, for offering a comprehensive report."

BK – So interesting, especially if the data that you're starting to look at, plays out… reads out as we get further down the line. If it's going to make a difference in terms of what treatments might be best for me, it's always good to have as much information, just like it's a no-brainer at this point to know if you're TP53 deleted or 17p deleted. That that's an important prognostic factor.

KS – You're absolutely right. But let me just support what you said by saying that one of these subsets, for instance, subset number two… it's essentially devoid of any TP53 defect, yet the outcome is as bad as TP53 CLL. So, shouldn't we want to know if the patient has that particular configuration in the immunoglobulin genes? Because the decisions about follow up and, as it

appears… but I should not disclose more information because we are currently analyzing this data. Our decisions about how to manage the patients would have been different.

BK – Doctor, thank you so much for that important research you do.

KS – You're very welcome, Brian.