You Are Not too Old to Get ZAPped!

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Welcome all who follow CLL research to Generation Z – ZAP-70, that is. Over the last few years our understanding of CLL has increased, disproving myths and resulting in newer and promising prognostic markers, classification systems, and therapies. These insights were included in the Education session on CLL (held yesterday and again today from 7:30 - 9:00 a.m.).

Dr. Nichlas Chiorazzi from the Feinstein Institute for Medical Research in New York discussed the biology of CLL and new data indicating that patients with CLL do not simply accumulate lymphocytes, but also have lymphocytes with rapid proliferation. "Traditionally CLL was thought to be a disease of accumulation – but it appears that it is not that simple," said Dr. Chiorazzi. He went on to explain that many indirect markers of proliferation also exist — CLL cells behave as dynamic cells that turn over at definable rates (that are more rapid than normal lymphocytes), they may not have an inherent apoptotic defect, and they have an emergence of more detrimental subclones. Furthermore, data from *in vivo* "birth" and "death" rates of CLL cells further support balance of accumulation and proliferation in this disease. Classifying patients according to more relevant biological markers will result in more accurate diagnosis, risk stratification, and decision making for appropriate therapy for patients.

Dr. Emili Montserrat from Barcelona, Spain, went on to apply much of this biology to help us understand the multiple prognostic factors in CLL. Gone are the simple number of lymphocytes, marrow pattern, and LDH. Newer markers include CD38, cytogenetic abnormalities like an isolated 13q deletion or the 17p deletion, ZAP-70, and immunoglobulin heavy chain rearrangement status. These are not boutique markers for academic purposes – they promise to predict response to therapy and to distinguish indolent versus aggressive disease, assisting clinicians in deciding when and how to treat. The challenge will be to ensure quality control and to make the needed tests available to clinicians. Time will also tell how they can be used to influence treatments algorithms – from "wait and watch" to chemotherapy to stem cell transplant.

But what do we do right now? Before validated models can be generated to use these new prognostic markers, clinicians are left with a huge spectrum of choice for therapy of CLL. Dr. William Wierda from M.D. Anderson Cancer Center reviewed the standard of care for CLL, but also gave us a look into the future of CLL. He told us about trials that are ongoing to determine which patients are at high risk for shorter survival and whether early intervention can improve outcomes. He discussed the need to identify targets for treatment in CLL, such as 17p; he also reviewed strategies for immunotherapy of the disease, with agents such as alemtuzumab. Furthermore, these newly recognized actively proliferating "young" CLL cells may be susceptible to vaccine strategies.

The times are changing in CLL – both in the way we think about the disease and how we treat it. Chronic doesn't mean old, so stay tuned to Generation Z and the evolving world of CLL.