



Advancements in Hematological Malignancies

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Welcome to a series net casts brought to you by Yale University.

Thank you for joining us for this edition of Yale Cancer Answers, where we provide you with up-to-date information on cancer care and research. Our host, Dr. Steven Gore, is Director of Hematological Malignancies at Smilow and an expert on myelodysplastic syndromes. He interviews some of the nation's leading oncologists and cancer specialists who are on the forefront of the battle to fight cancer. If you are interested in listening to past editions of Yale Cancer Answers, all of the shows are posted on the Yale Cancer Center website at YaleCancerCenter.org. If you would like to join the conversation, you can contact the doctors directly, the address is canceranswers@yale.edu. Here is Dr. Gore.

Gore Good evening. This is Dr. Steven Gore, and I am joined today by my guest Dr. Scott Huntington. Dr. Huntington is an Assistant Professor of Medicine at Yale School of Medicine in the Division of Hematology, and he is here with me tonight to discuss hematologic malignancies and particularly his interest in lymphomas. Scott, thank you so much for joining us tonight.

Huntington It's great to be here.

Gore Scott, how did you get interested in blood malignancies and how did you get into lymphoma?

Huntington Two major draws to the field, I had an early medical education where I had the opportunities to spend some time in a cancer clinic, a blood cancer clinic, and to witness those really rich and rewarding relationships between physicians and their patients, in that rather difficult period of cancer diagnosis and really guiding them through the therapy was really a rewarding experience and so that patient relationship drew me to this field. At the same time, the science behind cancer and the science behind advancing our therapies for cancer really was a twofold kind of link between the patients and the science and there really was no question early on that I wanted to be an oncologist and blood cancer specialist. In terms of lymphoma, the real draw there is that lymphoma can impact patients of all ages, so I have a very diverse patient population and the therapies are incredibly diverse and so every day there is something new, something exciting and it is a very multi-disciplinary field where we have our pathologist involved in terms of diagnosis, we have chemotherapy or therapies that are recommending and also radiation therapists as well coming together. So, it is an incredibly rewarding field to be in, and the scientific advances are really coming quickly so that the therapies are changing and improving clinical outcomes for the better.

Gore Is there more than one kind of lymphoma?

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Huntington Yes. Lymphoma is the most common hematologic malignancy, it is about 60% of all blood cancers and in terms of blood cancers, that represents about 10% of cancers. So, within blood cancers, lymphomas are the most common and there are many different types of lymphomas. We typically categorize the broader categorization to Hodgkin lymphoma and non-Hodgkin lymphoma, and within Hodgkin lymphoma, there are a few different varieties, most classically patients present in their younger, either late adolescence or younger adulthood. Whereas, non-Hodgkin lymphoma can be further divided many, many times over into T-cells and B-cells and within those there are many different subdivisions. And the therapies really depend on what subtype of a subtype of lymphoma that you have. And so, the pathology diagnosis and the clinical diagnosis really come together to form what the therapeutic recommendations would be for our patients.

Gore How do patients find out that they have a lymphoma? Why would you be worried about it or how do you come to medical attention?

Huntington The clinical presentation for lymphoma varies as well. There are very slow growing, what we call indolent lymphomas or low-grade lymphomas where our patients may be completely asymptomatic and the diagnosis usually comes incidentally. And so that means, on an annual physical exam, maybe a patient notices a lump and their provider recognizes that this is a new lymph node that is enlarged and that could lead to a diagnosis or potentially annual blood counts might be low and so that could lead to further workup. And then, finally, it is quite common that the patients are getting imaging for other diseases or other etiologies, whether it be a kidney stone or appendicitis and sure enough there are some lymph nodes that are there on imaging and further diagnosis could certainly define whether this could be an indolent lymphoma. On the other end of the spectrum are the more what we call aggressive or high tempo lymphomas where the patients really progress over weeks to months in terms of becoming symptomatic. And so, the symptoms associated with that, maybe a rapidly enlarging node or a lesion, profound fatigue or anemia where someone might be short of breath, really having trouble getting up to kind of start their day. There is also risk for low platelet count sometimes. So, these are the cells that stop us from bleeding. So, patients may have bruising or easy bleeding and then finally things like weight loss, poor appetite, fever, chills, night sweats. Those are the classic symptoms associated with more up-tempo or aggressive lymphoma.

Gore And while those symptoms are scary, I would think people get really frightened when they are losing weight and they are not trying to, or these night sweats which can be so uncomfortable and everything. The other thing you were mentioning earlier about the

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low-grade lymphomas being found on a scan, what a scary thought that you could have these enlarged cancerous lymph nodes and not know about it, is it not something that we should be scanned all the time for to get them out as quickly as we can?

Huntington That is a really good question. In terms of indolent lymphomas, the classic tempo is that really these things are forming over years typically. And when they do form, usually they remain asymptomatic until they develop either accumulation of cells that they are pushing on an organ that may be of importance or they are on the periphery, so we can feel these lymph nodes and they come to the attention of the patient. The thing about indolent lymphoma is that these are very slow growing and our therapies are highly effective, but the treatment actually cannot get rid of all the lymphoma cells. So, the indolent lymphomas generally are treated right before the patient becomes symptomatic. So, if we identify it, we actually do this thing what we call active surveillance. And we are looking at kind of the pace, defining the pace of the indolent lymphoma and really trying to treat before the patient might become symptomatic. That is really in stark contrast to the more aggressive lymphomas, where these aggressive lymphomas, the cells are really all replicating and so our traditional therapies that go after fast dividing cells have the potential to get rid of all of them. And we actually can cure a very high number of aggressive lymphomas, and so as soon as an aggressive lymphoma is diagnosed, we are more apt to really try to treat this aggressively with treatment. And again, for the indolent lymphomas, commonly we do this thing called active surveillance and we are really just watching the patient which can be very difficult for someone diagnosed with a new disease, they are told it is a cancer, but then we step back and say we need to watch this. In some folks, we can watch this for years and years and they will never need therapy. And so the real quandary is that we certainly want to treat patients if it is going to benefit them and improve their quality and quantity of life, but we also recognize that some patients actually may never need treatment and we would not want them to really have the experience of the side effect potential of our therapy. So, it is a bit of nuanced balance in terms of in lymphoma, there is a really large spectrum of clinical disease and the therapies really range from watching to more intensive treatments.

Gore It sounds like although you specialize in one particular group of cancers, it seems like in fact you are dealing with dozens of different things you need to know a lot about?

Huntington That is exactly right.

Gore Fascinating. And is there any way in these lower grade lymphomas to study them to know which patients are more likely to have earlier progression or more likely to never need to be treated. Is there something people are trying to figure out?

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Huntington We should take a step back and discuss how we diagnose a lymphoma. So, typically lymphomas, they do involve the lymph nodes. We do occasionally have what we call extranodal or lymphoma that affects outside the nodes, but really the way that we diagnose is with a biopsy. Ideally, we take out the area of the lymph node, a small piece, to look at it under the microscope, and that helps with the diagnosis, but there are a number of other things that we are learning about lymphoma and cancer in general, which is really trying to figure out what are the drivers behind our cancers. And so, in some lymphomas, we can actually find early drivers that may portend a more aggressive disease course. And we may find things that actually predict a response to one therapy or the other. So, within a single type of lymphoma we are further sub-characterizing based on kind of the molecular markers and that really is going to have a pretty large impact on treatment going forward, helping stratify risk but also trying to predict which therapy is the correct approach for an individual patient. So, personalized medicine is really coming to lymphoma at a rapid pace.

Gore Are there tests that can be helpful in choosing therapies, selecting therapies or in terms of prognostication, are they now standard part of diagnostic workups in most pathology labs?

Huntington They are growing. Yes, they are a growing phenomenon really not only in academics but outside where for instance for chronic lymphocytic leukemia or small lymphocytic lymphoma, there are genetic mutations or what we call translocations that are basically rearrangements of common proteins that really should be done in all patients with diagnosis because they really have a large impact on therapeutic choices, not only on risk stratification but really patients with certain type of CLL seem not to respond as well to chemotherapy and really should be getting novel, what we call novel or oral agents that are more targeting the drivers behind the CLL as opposed to traditional chemotherapy, which is really about going after cells that are dividing and leading to cell death that way.

Gore When you just say drivers, you are talking about mutated genes and proteins that biologically affect the cells, is that right?

Huntington Exactly, yes. In terms of many lymphomas, the major driver is a downstream of what we call the B cell receptor and so many of these genetic aberrations are basically driving the B cell to replicate to continue to accumulate as opposed to what is supposed to happen is that these cells eventually have a switch that allows them to die, and so the on switch is basically left on and these new treatments are trying to kind of sequel and swash that on switch.

Gore Turn the on switch off?

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Huntington Exactly, yeah.

Gore Forgive my ignorance, what is a B cell, Scott?

Huntington In terms of lymphoma, we classically subdivide into two, T cells and B cells. B cells are really all about the path towards what we call antibodies, which are what our body makes in response to seeing proteins that they do not like.

Gore Like infections?

Huntington Infections, vaccines, so when you get your annual influenza shot or your pneumovax, it is really about the B cells making an antibody response. The T-cells on the other hand are a very diverse field of lymphocytes that have a number of functions in terms of allergies, in terms of allowing us to see the world in kind of the correct way, so not overreacting to every food antigen but also in controlling when things get out of hand or have cell damage, the T cells are really important. And so, both T cells and B cells can beat the lymphoma and the therapy for those are quite different and that is kind of the difference between B and T cells.

Gore When you are talking about these B-cell lymphomas, you are talking about lymphomas that are related to these antibody-forming or the precursors to the antibody cells, is that right?

Huntington Exactly.

Gore How is the field changing? You mentioned that there are new treatments or oral treatments. What is going on that is new and how would people know about that stuff?

Scott I think the major driver of clinical changes and what we are doing for our patients is better understanding of the disease themselves. So, recognizing that given what we thought was one kind of basket of lymphoma diagnosis is really a number of sub-classifications where there are different drivers within the lymphoma, and recognizing that we are able to bring in different therapies to either target that driver or combining our traditional therapies to really improve both the responses, so getting into a nicer response or deeper response and hopefully increasing the chance of cure for many of our patients.

This has been another edition of Yale Cancer Answers. We hope that you have learned something new and meaningful. If you have questions, go to YaleCancerCenter.org for more information about cancer and the resources available to you. We hope that you will join us again for another discussion on the progress being made here and around the world in the fight against cancer.