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Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer.

This week, it’s a conversation about lymphoma with Dr. Shalin Kothari.

Doctor Kothari is an Assistant Professor of Medicine and Hematology at the Yale School of Medicine where Doctor Chagpar is a Professor of Surgery.

Start by telling us a little bit about yourself and about what you do as a hematologist and oncologist.

I joined Yale Cancer Center three months ago and my specialty and my focus is lymphoma, lymphoma patients, treating them and researching newer therapies for lymphoma.

Tell us a little bit more about lymphoma.

Yeah, you’re right. There are approximately 65 different types of lymphomas.

So when we talk about lymphoma we really have to get granular because every different type of lymphoma has a different treatment, and many times we can even wait and watch.

So it is very important to figure out what the sub type of lymphoma is before jumping to any therapies.

And one of the things that is very important to keep in mind is that lymphomas usually require a big chunk of tissue for a good diagnosis.
So one of the things that typically can go wrong and does go wrong frequently at centers is that we don’t have enough tissue, and that’s why we are left in the dark as to what the exact diagnosis is.

But to tell you what lymphoma is in general, lymphoma is essentially a cancer of immune cells and immune cells live in different areas of the body, such as lymph nodes. And one of the biggest lymph nodes that we have in our body is the spleen, and in the belly and sometimes even in the liver. So these are the most common sites where lymph nodes can get enlarged and that can lead to lymphoma.

How do people present with lymphoma? I mean do they present with big lymph nodes? That is one of the possible signs or symptoms rather but it can also present as just a very subtle blood abnormality. Which is detected by a blood test. The symptoms range from fevers, night sweats, weight-loss along with a swollen lymph node. Either it could be in the neck, it could be in the chest, or it could just be as indolent as just a small abnormality in the blood that can only be detected by a blood test. Many of those, the latter types of lymphomas, are detected by a routine blood test that was done. It is more often an incidental finding. In either case, how do you make that diagnosis?

You mentioned that you would need a sufficient amount of tissue if you just had a routine blood test, you’ve been feeling a little under the weather, maybe it’s just a cold and feeling a little rundown,
a little tired.

I’ve got a bit of night sweats and fevers, but I thought it was a cold.

So I went to the doctor, he drew some routine blood tests and now you’re telling me that he suspicious of lymphoma.

How do we get from that to actually making a diagnosis?

That’s a great question. Typically we start with a blood test, but before that the doctor that you are going to see would do a full physical exam.

So one of the things that if the patient is not complaining him or herself, then they would do a full physical exam to make sure that there are no swollen lymph nodes.

Typical areas that we look at our the neck, under the armpits or at the groin crease so there are these typical areas that we look for lymph nodes and then we do a comprehensive lung and abdominal exam, so that is just to look at whether there is anything swollen.

We can feel just by hand.

But then the next steps are to look at different sub types of white blood cells and look at whether they are increased in number or do they show any signs of markers on the surface of the cells which shouldn’t be there.

And that’s another blood test, correct? And so you do that, and then what happens?

Well then we figure out what type of lymphoma it is.
As I said before there are 65 different types of lymphomas as given by WHO classification, so it is absolutely crucial to figure out what the type of lymphoma is and that happens by putting together the entire spectrum of data. So that includes the way the patient presented, what are the symptoms? What did those tests in the blood show and also the biopsy specimen? We put all three pieces of information together, figure out the subtype, figure out the stage of lymphoma, and decide whether we need to treat the patient or not.

You’re feeling a little under the weather, they did a routine blood test, they said, your white count is out of wack, they said, your lymph nodes were not swollen up, the most common type of lymphoma that presents the way you described is CLL. Chronic lymphocytic leukemia, where the lymphoma cells are circulating in the blood so there is nothing really to biopsy. We just acquire a few tubes of blood and do all the tests that we would have done on a biopsy specimen but on a blood specimen instead.
Sometimes we also have to do a bone marrow biopsy which is a test looking at the hollow part of the bone that’s the factory of all the cells that I just described that can become cancerous but you know the field is trying to move away from doing bone marrow biopsies because our tests in the peripheral blood and tissue are getting more and more sensitive. We can get most of the information that we need but that being said, there are still many situations where we have to do a bone marrow biopsy.

And so if somebody presents on the other side of the spectrum, feeling terrible, fevers, chills, night sweats, losing weight for no reason, notices a lump in the neck, then feeling more lumps in the groin, you go to the doctor, and the doctor gets worried.

What then? Do they do a biopsy of the lymph nodes? Is that how that works in that scenario that you’re describing?

Biopsy becomes very, very important and we work very closely with our interventional radiologists or even surgeons sometimes, depending on the location of the swollen lymph node.

So either surgeons or an Interventional Radiologist would biopsy the specimen, and then that specimen would go to the pathologist who would look at that tissue under the microscope, stain it with different markers that we already know may be positive in these different types of lymphomas,
and then we figure out the subtype of the lymphoma and within usually within a week or two we are ready to start the therapy.

If the patient is really sick at that time, sometimes we even have to admit the patient while all these results are back and just give some medications to temporize rather than starting full blown therapy that we would have given that we would give in the future.

So what’s the most common kind of lymphoma? I mean, you say there’s 65 different types, your head could spin, especially with all of the different therapies. If each one of these is treated differently, what’s most common?

That’s also a tricky question to answer, and the reason is that we branch the way we classify lymphomas. The broad categories are Hodgkin lymphoma and non Hodgkin's lymphoma, but then it gets complicated very quickly so that classification, Non Hodgkin Lymphoma, is the most common, so how do you know what’s a Hodgkin’s lymphoma? What’s a non Hodgkin’s lymphoma?

Hodgkin’s lymphoma has a very classic appearance on the tissue biopsy specimen, so that’s something that the pathologist would tell us that it is either Hodgkin or non Hodgkin lymphoma. And you were saying Non Hodgkin’s is the most common right? So pretty much everything else falls under Hodgkin’s.
The way I like to think about it is what is the origin of the cancer cells? There are different types of lymphocytes. The immune cells that we talked about before, so it could be B cell or a T cell. There are Non Hodgkin’s lymphoma’s that originate from a B cell, so they’re called B cell lymphoma’s. Those that are Non Hodgkin Lymphoma that originate from T cells and they’re called T cell lymphomas. Then the way I think about it next is under B cell lymphoma, which is the most common out of B and T cell lymphomas, is looking at whether they’re aggressive in presentation or indolent in presentation, so that’s how I like to broadly classify them. And when we had talked about that first case, which was really indolent cancer where somebody was picked up on a routine blood test, you called it CLL you called it a leukemia. What’s the difference between a leukemia and a lymphoma or are they the same? They are not the same, but this leukemia in general, means that there are cancer cells circulating in the blood and most of the time when we talk about the routine leukemias, I don’t treat leukemia patients, but CLL is an exception because that particular type of cell circulating in the blood is a lymphocyte, but it has not honed into a lymph node or something that is tangible or can be seen on a physical exam.
So that’s why it’s sort of not really a misnomer, but it can get people confused.

You had mentioned earlier that 65 different types of lymphomas are all treated differently, and for some of them you can actually just watch them.

That is correct, and that’s exactly why the classification and working very closely with the pathologist is absolutely crucial.

The subtype that we talked about, CLL, many times we can just wait and watch.

And one of the things we want to look at is whether the cell burden, the cancer cell burden in the body is large enough to either compress on our normal organs or prevent production of other cell lines such as platelets or red blood cells. So if we see those signs, then that’s when we pull the trigger to start the treatment.

But many of the times, particularly for CLL, we can wait and watch.

But that being said, there are many other indolent lymphomas such as follicular lymphoma and even very minor subsets of mantle cell lymphoma.

Lots of great information, but we’re going to have to take a short break for a medical minute.

Please stay tuned to learn more about lymphoma and early phase clinical trials with my guest.

Doctor Shalin Kothari. Support for Yale Cancer Answers comes from AstraZeneca dedicated to providing innovative treatment options for people living with cancer. Learn more at astrazeneca-us.com.

This is a medical minute about melanoma.

While Melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. When detected early,
however, melanoma is easily treated and highly curable. Clinical trials are currently underway to test innovative new treatments for melanoma. The goal of the specialized programs of research excellence in skin cancer, or SPORE grant, is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improved diagnosis and treatment. More information is available at yalecancercenter.org. You’re listening to Connecticut Public Radio. Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by my guest doctor Shalin Kothari. We’re talking about lymphoma and early phase clinical trials. Now, right before the break, Shalin was telling us about lymphoma being this really large basket of 64 different types of cancers, essentially all of which are bound together by this term lymphoma. Because they are cancers of lymphocytes, those immune cells that all of us need to help fight infections. Some of these present in a really indolent fashion, some of them present with symptoms of fevers and night sweats and weight loss and enlarged lymph nodes, and even getting your spleen enlarged. And we talked a little bit about how the diagnosis can sometimes be made on something as simple as a routine blood test, but other times really requires a tissue biopsy. Right before the break you were saying that some cancers don’t require any treatment and that you can simply wait and watch. But other cancers do require treatment.
Can you tell us a little bit more about how lymphoma is classically treated and a bit about some of the research that’s going on in terms of treatment of lymphomas?

Classically lymphoma is treated, and it becomes a bit challenging because every subtype is again treated very different,

but let’s say we talk about B cell lymphoma’s, then most of the regimens that we use for the first year as a frontline therapy for the patient,

we would use a antibody drug called Rituximab or a CD20 antibody,

which is one of the very common markers on B cells. So are these like chemotherapies? Is that what it is? I would say they are more of a protein infusion.

That particular drug that I talked about is not a chemotherapy, but it is typically combined with two or three or even four different types of chemotherapy drugs in combination.

So usually we have to find different ways to trick the cancer cell into dying, and that requires different tools,

so that the cancer cell is attacked from different angles. That’s why we combine these therapies together as a cocktail which has been studied for many years,

and we have a good idea of what goes with what and what regimen,

what cycle, how many cycles,

how many weeks of a break,

all of that has been figured out over a period of time and that is a good segue to what you were asking me about the research.

All of these questions as to what drug to use,

how do cancer cells figure it out?
A way to survive with these therapies and what is the dose of the drug to use?

What is a dose of a drug that doesn’t cost too much toxicity through the patient?

What is the schedule of that combination of drugs?

All of that is studied in clinical trials, so, for example at Yale for lymphomas, we have around 60 to 70 different types of clinical trials ongoing.

And they can range from early phase clinical trials, to late phase clinical trials.

And my team, we are actively involved in enrolling patients into these clinical trials so that they can benefit and they can help other patients benefit in the future because any therapy that we use today at some point in the past was studied as a clinical trial which is now benefiting everyone who has lymphoma.

But a lot of patients may think, I just want what is standard.

I don’t want to be a human Guinea pig.

Somebody else can be a human Guinea pig.

How do I know that what you’re giving me is going to work?

Or is going to work better than standard? What do you say to patients who say that?

That’s an excellent question and a lot goes into research before we decide to introduce the drug as a clinical trial. Typically a drug is studied for years and when I say years, it could be even a decade or at least four to five years before we even think of designing a clinical trial for use in patients and the way we do that is,

we start with testing lymphoma cells with that drug in a Petri Dish in a Translational Research Laboratory.

And then we move on to
lymphomas in mammals. So we use either mice or other mammals just to see what the drug does in those animals through those phases, and we figure out the dose, or at least the range that we should study in humans because we have a lot of formulas and calculations that we can do to figure out where to start as a starting dose for the drug in a particular patient. So with all of these different types of lymphoma and all of these different therapies, what do you think is the most exciting in terms of where research is going? The research is definitely moving towards using less and less of what you described as chemotherapy, which of course is very effective in killing cancer cells, but it can also cause other unwanted toxicities and the research is moving very very fast towards using novel therapeutic agents which really look at genetic and even cellular level to figure out what exactly is driving the cancer cell. What is that genetic change that is leading that cancer cell to go from 2 cells to four cells, and once we figure that out, we can use a drug that directly targets that particular mutation, or a pathway that we think is crucial for that cancer cell to survive. So as you can imagine, if we are that selective then we can reduce the toxicities that drug would cause otherwise.
sense. That’s like all of this personalized medicine that people are talking.

Yes in some ways, yeah.

Tell us about your research. Do you work in that field?

Yeah, I dedicate 50% of my time into a translational research laboratory where I study mantle cell lymphoma.

We’re trying to figure out newer therapies for mantle cell lymphoma, which is a subtype of aggressive B cell lymphoma’s for the most part.

And currently there are a couple of drugs that are already known, these novel therapies that are already known to be active in mantle cell lymphoma, but many or most versions will eventually develop resistance to those drugs, so we have to find newer therapies that will work after those two drugs or three drugs stop working.

So that’s what my focus is in the research laboratory to figure out.

And how do you do that? As I discussed before, we take lymphoma cells in a Petri dish, one of the first steps that we start with and we first figure out what is driving the cancer cell to divide.

So then we get, let’s say a list of 10 different genes and five different pathways to target. Then we look at previous research that has already been done and see what can we target in that pathway and then try to design either a designer drug or collaborate
with other laboratories around the world that have already designed a drug for that particular pathway and see if that works against the lymphoma cells.

When you say that you’re trying to find therapies that will help in the cases of resistant lymphoma, when you’re looking at pathways that cause cancer cells to divide, I would think that those would help even up front as frontline therapies do.

Do you try to figure out why they were resistant to the first line chemotherapy or the first line drug?

Because presumably those already were targeting certain pathways that made cancer cells divide to begin with.

That is true, and that really, again depends on the type of lymphoma.

For example, mantle cell lymphoma is the frontline therapy that we use even to this date with Rituximab that I talked about in combination with other chemotherapy agents and to be honest, most of the lymphoma frontline therapy is still that cocktail of chemotherapy with Rituximab, and for good reason the bar is so high for these novel therapies to be used in front line. We don’t want to harm patients.

We have to find those novel drugs that will either improve, further the response to the frontline therapy and if not, then most most of the time they end up being used in second or third line.

If the patients develop resistance to the frontline therapy.

How often do patients with mantle cell lymphoma actually become resistant?

Mantle cell lymphoma is one of the areas where there’s a lot of research that needs to be done.
I would say almost 70 to 80% of patients develop resistance to the frontline therapy. And as you can imagine, we already know that’s what to use in second line third line. But then eventually most patients develop resistance to all these lines of therapy.

And why is that? That’s the $1,000,000 question. It’s not easy to figure that out, but we do know that there are different mutations that the cancer cell can keep evolving. That’s probably the best way to think about it.

So if you introduce frontline therapy to a cancer cell, and let’s say there are 10 cells to kill, maybe 8 of them get killed but the other two they find a way to change their path of dividing and circumvent the way the frontline therapies worked. So now they have become smarter. They have acquired new mutations, new genetic changes that weren’t there the first time and then you introduce second line therapy and again, the same thing happens where you kill most of the cells but not all, and then those few cells that are left behind, they eventually start dividing again because they have acquired newer mutations.

It sounds a lot like what our audience might be familiar with in terms of antibiotic resistance that you see one antibiotic and the idea is that you don’t want to keep taking different antibiotics, especially when you don’t need them. Because then you have the generation of super bugs that are resistant to all antibiotics.
Is that a similar kind of concept?

Similar concept, but we are not worried about a generation of superbugs in this case because most lymphomas if not treated can be deadly.

If they need treatment, if they’re aggressive kinds of lymphomas, and if they are not treated, they can be deadly, so we don’t typically worry about what will happen to that cancer cell, and what different types of mutations they’re going to acquire.

Because we really don’t have the time in that particular patient, so in other words, we typically switch from one line of therapy to the next line of therapy very quickly.

The moment we know that this particular patient’s lymphoma stopped responding, then we quickly move to the next line because it’s crucial to try to keep it at a very low level of burden or even completely cure it.

Doctor Shalin Kothari is an Assistant Professor of Medicine and Hematology at the Yale School of Medicine.

If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at Yalecancercenter.org.

We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public Radio.