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00:00.000 --> 00:08.800 Support for Yale Cancer Answers comes from AstraZeneca, providing important treatment options for various types and stages of cancer. More information at astrazeneca-us.com.

00:08.800 --> 00:44.700 Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. 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 is a conversation about pediatric CAR T-cell therapy with Dr. Niketa Shah. Dr. Shah is the Director of the Pediatric CAR T-Cell Program at Smilow Cancer Hospital and an Associate Professor of Pediatric Hematology and Oncology at Yale School of Medicine, where Dr. Chagpar is a Professor of Surgery.

00:44.700 --> 01:05.600 <vChagpar>Let's start by talking about what exactly is CAR-T. I mean, it is a buzz word that many people in the medical scientific field have heard about, kind of as one of these latest and greatest things, but the general public may not exactly know what this is, so can you explain it to us?

01:05.600 --> 02:38.500 <vShah>Yes, I can. For many, many decades, the main frontline treatment for cancer has been three things: Surgery, radiation and chemotherapy. A couple of decades back, we got the option of targeted therapy with imatinib for one type of leukemia which directly targets the cancer cells and in the last decade, there is a newer frontline, which we now call the fifth arm of cancer treatment, and that is to help a patient's own immune system target and kill their own cancer cells. It was introduced by many simultaneously and it was worked up at many centers, but the University of Pennsylvania was one of the pioneers in working with one type of leukemia where they introduced this CAR T therapy, where its full form is Chimeric Antigen Receptor T-cells. We have 2 types of lymphocytes in the body - one is T-lymphocyte, which sometimes we call terrific cells, terrific lymphocytes, and the B-lymphocytes, which produce some proteins also called antibodies which help us fight infection and that we use for some of our vaccines.

02:38.500 --> 02:42.700 <vChagpar> So, T-cells and B-cells, when you say lymphocytes, you mean like they are immune cells?

02:42.700 --> 03:13.500 <vShah> Yes, these are the 2 immune cells, particularly the white cells, the white blood cells of our body and they are helping us to fight some of the infections and now in T-lymphocytes, scientists have added in the lymphocyte itself, and that lymphocyte is capable of fighting certain types of leukemias.

03:13.500 --> 03:44.700 <vChagpar> So you are born with these white blood

cells and your bone marrow makes these white blood cells? And it makes some B-cells and it makes some T-cells, and those B-cells and T-cells, they usually fight infections and things. I think we all understand that part, but how do you get a T-cell to get a protein added on to it that can attack a leukemia?

03:44.700 --> 04:56.900 <vShah> You collect a patient's own T-cells first from their blood. You collect the patient's own immune cells. In the laboratory, you specifically engineer, reprogram those T-lymphocytes by adding some nontoxic viruses and you use that media to introduce that protein into those T-lymphocytes which will create specific receptors on the surface of those T-lymphocytes and you expand those, so you make many more of those T-lymphocytes or the immune cells and you give back those genetically modified T-lymphocytes to the patients and in patient's blood where those leukemia cells are floating away, and those leukemia cells have also the target on their cell surface, which will be recognized by this new T-lymphocytes which is now CAR T, Chimeric Antigen Receptor-Added T-cells. They will recognize those receptors on the patient's leukemia cells and they will fight and kill those leukemia cells.

04:56.900 --> 05:52.500 <vChagpar>I want to take everybody back to junior high immunology. Because it has been a while for me and it might have been a while for our listeners as well. So, normally, when your T-cells are fighting infections, like you get a cold or something, the T-cells are roaming around in your bloodstream and they notice Aha! you have got a cold virus or something and your T-cells will say, that is not supposed to be there and so will recognize it as being foreign based on these receptors and once it has a receptor that recognizes something as being foreign, then it can kind of prime your immune system to go and attack that and get rid of that virus. Is that sort of how it works?

05:52.500 --> 05:55.900 <vShah> Yes. And that same approach is being used to kill the cancer cells.

05:55.900 --> 06:27.700 <vChagpar> So, when you do this, you are taking a patient's blood and in that blood there are some T-cells and so in the lab, you are taking the patient's own T-cells which normally would not have a receptor to leukemia because your T-cells are not thinking, yeah this person is going to have leukemia, but you are introducing to that T-cell in the lab, in the petri dish, these leukemia cells, based on a virus.

06:27.700 --> 06:44.600 <vShah> We are not introducing the leukemia cells into those patients T-cells, we are specifically introducing certain proteins and a certain type of receptor which will recognize those leukemia cells.

06:44.600 --> 07:12.200 <vChagpar> Exactly. So, it is introducing the T-cells to proteins that will help the T-cell recognize the leukemia. I guess the first question is - are all leukemia proteins going to be the same, like if you introduce a protein to a particular T-cell and you say okay T-cell, this is the protein on

the leukemia cell we want you to target, you will have to be pretty damn sure that that patient has got that protein?

07:12.200 --> 07:51.100 <vShah> Yes. CAR T cells are not useful for all types of leukemias. There are different types of leukemia and we identify based on their surface receptors, and we have numbered them in cluster differentiation and we call it, particular CAR T cells which are right now developed for cluster differentiation or CD19 type of leukemia. So, if the patient has CD19 positive leukemia, these CAR T cells will recognize those leukemia cells and will target them.

07:51.100 --> 08:04.300 <vChagpar>So, in order to do this, you must have also taken a blood sample or bone marrow sample or somehow figured out what kind of leukemia the patient has.

08:04.300 --> 08:21.400 <vShah> Patient has, yes. We need to first and then only if the patient has CD19 positive leukemia, then we can generate patient's own blood immune system the CAR-T cells which can target their own CD19 positive leukemia.

08:21.400 --> 08:27.800 <vChagpar> Because that CD19 is a surface marker on the leukemia cells?

08:27.800 --> 08:31.500 <vShah> Yes. So, that is one of the identifying marker on those leukemia cells.

08:31.500 --> 08:38.200 <vChagpar> Gotcha. So, once you take a sample of the patient's is it blood that you find it in or bone marrow?

08:38.200 --> 08:40.400 <vShah>Mainly bone marrow.

08:40.400 --> 09:07.000 <vChagpar> So, you take a patient's bone marrow and you see what kind of leukemia they have and you look for these surface markers and you find out that they have got CD19 as a surface marker, and then you say, we have technology that we can introduce to your T-cells - the CD19, so that your T-cells get primed in the laboratory against CD19.

09:07.000 --> 09:09.400 <vShah> Yes. So, against CD19 positive leukemia cells.

09:09.400 --> 09:20.300 <vChagpar> So, then you take the patient's T-cells and you genetically kind of modify them, how exactly do you do that?

09:20.300 --> 11:13.400 <vShah> So, it is a whole process. So, once we identify that this patient has a resistant or relapsed CD19 positive leukemia cells which is not responding to the usual line of treatment or the patient has relapsed after chemotherapy or even after bone marrow transplant, then we collect patient's cells from their blood. So, it is like a process where the patient's whole blood volume passes through a machine and then we just collect the cells which we want and the rest of the blood goes back. And so, we collect certain number of cells and then we send it to the laboratory. In the laboratory, they first prepare those modified cells with the help of gneetic engineering with the help

of nontoxic virus and then once the set of cells are prepared, they expand, so they make millions of those cells and that process takes, previously it was taking weeks, now they have limited and they learnt how to make it faster, so within 3-4 weeks we can make those cells, and then once we know that those cells are developed and we have enough cells, we to the patient give them little bit of chemotherapy so that their immunity is little down and the cancer cells are also little bit under control so when the new cells come in, they are not rejected by the patients because these are now, even though they are their own cells, they are little bit different right and anything which is foreign, our body tries to fight back right. So, then we give those cells to the patients and those cells will over certain time period will fight those cancer cells and then they need to be in the body for a long time so that new cancer cells are not developed.

11:13.400 --> 11:54.500 <vChagpar> Okay, a whole bunch of questions. First question, this whole genetically modifying your own T-cells, I can imagine that many of our listeners might be going, wait, wait, wait a minute, you are going to genetically modify my cells and then put them back in my body, that sounds a little bit like the Judsons and how do I know that this is safe and how do I know that with these viruses that you are going to introduce this protein into these T-cells that that is not somehow going to end up hurting me down the line, like how do I know that genetically modificed anything is okay?

11:54.500 --> 12:30.700 <vShah> So, these are, we are not genetically modifying their nucleus or anything, we are just introducing this, again these are the viruses which are dead cells only. They are not active viruses, we are just using their mode to introduce that little protein which will just produce on the surface of the cells only. They will produce extra little receptor so that, it is like the 2 arms they are adding to those cells. So, when those cells go into the patient's body, they will catch those leukemia cells, engulf them and kill them.

12:30.700 --> 13:20.500 <vChagpar> So, essentially it is all we are doing is taking your own cells and just like your own cells would have been introduced to a foreign antigen in your body, we are introducing them to a foreign antigen in the lab and then putting them back in the body. So, how come your immune cannot do that in its body all by itself? Like, I mean your T-cells go and attack the flu cells or other foreign cells and they do that just fine without us having to do anything in the lab, how come your T-cells cannot attack cancer cells all by itself, how come we need to do this bit about taking your T-cells out and introducing them to the antigen in the lab and then getting the receptor and then putting it back in the patient? How come the patient cannot do that by themselves?

13:20.500 --> 13:57.400 <vShah>So, that is a very good question. However, we have seen leukemia for the treatment, if it was, our body was, reacting like that, we will not need even the chemotherapy or any medicine to kill those cells. These cancer cells or the leukemia cells are so tough and they are the mutant cells which our body has produced, which were not recognized by our own immune system over time, and so our own immunity, normal immunity,

they do not have that capacity to target our leukemia cells.

13:57.400 --> 14:10.600 <vChagpar> Interesting. Well, we are going to have to learn more about these sneaky little leukemia cells and how CAR-T is a novel therapy that might actually help some patients right after we take a short break for a medical minute. Stay tuned.

14:10.600 --> 14:30.000 Medical Minute Support for Yale Cancer Answers comes from AstraZeneca, a global science-led biopharmaceutical business committed to bringing to market innovative oncology medicines that address unmet needs for people living with cancer. More at astrazeneca-us.com.

14:30.000 --> 15:19.900 This is a medical minute about pancreatic cancer, which represents about 3% of all cancers in the US and about 7% of cancer deaths. Clinical trials are currently being offered at federally designated comprehensive cancer centers for the treatment of advanced stage and metastatic pancreatic cancer using chemotherapy and other novel therapies. FOLFIRINOX, a combination of 5 different chemotherapies is the latest advance in the treatment of metastatic pancreatic cancer and research continues at centers around the world looking into targeted therapies and a recently discovered marker HENT-1. This has been a medical minute brought to you as public service by Yale Cancer Center. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

15:19.900 --> 16:15.800 <vChagpar> This is Dr. Anees Chagpar, and I am joined tonight by my guest Dr. Niketa Shah. We are talking about CAR-T cell therapy in terms of leukemia, particularly in pediatric patients. So, right before the break, Niketa was telling us about this new therapy - CAR-T, where essentially we take patients T-cells, your immune fighting T-cells in your body and we in the lab can make them recognize leukemia cells, which may have developed kind of an invisibility cloak that helps us, the immune system not recognize, I mean your body itself. So, really getting your immune system to say - hey, this really is foreign, it is not going to sneak under the radar and allow that T-cell to then attack the leukemia, did I get that sort of right?

16:15.800 --> 16:21.100 <vShah> Yes, that's correct, yeah.

16:21.100 --> 16:26.300 <vChagpar> So, it is really interesting technology and you said that this now can be done over weeks.

16:26.300 --> 16:59.700 <vShah> Yes. The first pediatric patient, she was treated by this mode of therapy in 2012 and since then many, many clinical trials have undergone to see whether this mode of therapy is working and that led to, because the success rate was so high, we got the FDA approval of this mode of therapy in 2017. So, now we call it as a living drug.

16:59.700 --> 17:01.800 <vChagpar> Because you are using your own cells.

17:01.800 --> 17:21.300 <vShah>Yes, so that is what, it is called now the living drug and it has helped us to fight some of the cancers, mainly in pediatric,

pediatric leukemia where previously we were not able to even control that. We were not even able to offer any hope to the patients.

17:21.300 --> 18:06.000 <vChagpar> So, I have a few questions. Another thing that you mentioned was that really you are using this therapy in people who have failed other modalities. They have failed standard chemotherapy, they have recurred, but if this is so good in terms of a therapy and if it really is "the living drug" such that you are using your own cells to attack these leukemia cells and if it can be specific because it is for a specific antigen on the leukemia cell, the CD19, why would not you use it first line, why would you have to wait and see if you failed other lines of therapy?

18:06.000 --> 21:00.900 <vShah>Yes. So, that is a really good question, and to answer that, I have 2 different things to tell. So, one, yes it is so simple as I mentioned, but it is in reality it is not simple because once we give these CAR-T cells, because these are immune cells, the therapy is not without side effects. So, the therapy has some of the serious side effects, which we need to carefully monitor - one is called CRS, cytokine release syndrome. Once these new modified immune cells enter into the patient's body and when they are doing their job, when they are targeting those leukemia cells, there is a release of different types of cytokines and that cytokines sometimes if it is a surge of those cytokine release, can develop severe high-grade fever, decrease the patient's blood pressure, respiratory problems and sometimes patients need to be shifted to the ICU, intensive care unit, and need to be monitored. Also, there are chances of some neurotoxicity. There are chances of developing little confusion and seizure-like activity. Again, that is short lived, it is reversible and short lived, but that time period, we need to monitor patients carefully. So, the whole team needs to be prepared to handle this CAR-T cell therapy, which, yes it is successful, it has an almost 80% success rate, but we need to monitor and develop this whole team and then there is also little bit chance of long-term side effect because these immune cells are targeting CD19 types of cells. Now, CD19 cells lies on the B-cells and the patient has a B-cell leukemia which is expressing those CD19 cells, but these modified cells does not know is it the CD19 B-cell leukemia or the CD19 normal B-cells, so they will wipe out the patient's B-cells so the patient needs to get immunoiglobulin lifelong just to revise, B-cells produces the protein which is called immunoglobulin which also help us fight against infection. So, we need to make sure patients receive immunoglobulin afterwards. So, these are 3 main side effects, which can occur in patients receiving the CAR-T. Most of the centers now have developed a team and trained their whole team, not only their pediatric bone marrow transplant team, hematology-oncology team but also the nursing team, neurology team, intensive care unit team to make sure the whole team is ready to handle if the patient develops this type of complication.

21:00.900--> 21:44.000 <vChagpar>And so, the complications are really because you kind of incited this massive immune response against the leukemia? So, another question I had was, okay you take out some of the T-cells from the

patient's blood, but the patient still has their own T-cells and the ones that you take out, you have modified so that they can recognize the CD19 and yes you expand the number of those and you give them back to the patient, but the patient still has their own non-CD19 mutated T-cells floating around, but it does not really dilute the effect?

21:44.000 --> 22:09.900 <vShah> No, because these cells are directly targeting just the target cancer cells, so that we do not need whole, and we are manufacturing enough so that they can target those cancer cells. However, your question is very important here that sometimes it is very important that not only we give those cells, those cells need to be persistent in the body.

22:09.900 --> 22:15.100 <vChagpar>And that was going to be the next question, is that you know cells die over a period of time and presumably these ones do too.

22:15.100 --> 23:00.400 <vShah> Yeah, and particularly if as you say that if is there a dilution effect or something that patient's own T-cells are also affecting them, so over time and that researchers have looked into this and they are now slowly and slowly modifying the techniques so that those cells are strong, so that they are adding some or changing those which proteins which we are adding into those cells so that they are creating those receptors which are going to target the patient's leukemia cells strong so that they target and kill them and also they remain in the system for a long, long time so even if there is a slightest chance of recurrence, relapse coming back, those cells are there still floating around.

23:00.400 --> 23:30.500 <vChagpar> So, tell us a bit more, speaking of that, about the time line of therapy. So, you have your initial dose of CAR-T therapy and then do you get like re-dosed, you know how with chemotherapy you will get certain cycles, you will get every week or every 3 weeks or whatever, with CAR-T therapy do you get like, you know we are going to give CAR-T cells now and then we are going to wait and we are going to give you an extra dose in a month or something like that?

23:30.500 --> 25:17.000 <vShah> No. So, when we give first time the CAR-T, we do not have that expectation we will have to repeat the dose because we want those cells itself to last longer. However, in very few cases where they do not last longer and if the patient has not developed any side effects or something and tolerated those cells well and if we have still leftover patient's own cells right because we created from the patient's own cells, so we have, we can consider giving them back those second re-infusion but most of the time, we try to just give one time therapy because sometimes it is also difficult to collect those cells also, immune cells from the patient because we should not forget those patients where we collect their own normal immune cells, they have previously received many heavy doses of chemotherapy. So, their immunity is also a little bit tired right? So, we need to make sure we are collecting enough cells. In few of the instances, we do face difficulty in collecting before even modifying those cells, we need to collect x number of cells from the patient right, and we are facing some

challenges that we cannot even collect the good number of cells. So, that will go back to your question which you asked earlier that if this therapy is working, why cannot we just use it in the frontline and that way I think as a physician I am looking at, that the treatment of leukemia and even not leukemia, some of the cancers will change in next 5 and 10 years where we will be using this CAR-T cells upfront.

25:17.000 --> 25:20.700 <vChagpar> Because you can take more cells when they have not been treated with chemotherapy upfront?

25:20.700 --> 26:23.200 <vShah> Yes so that will. And so, to again mention that right now we have the FDA approval of this living drug - CAR-T cell for pediatric for resistant or relapse CD19 positive acute lymphoblastic leukemia; however, there are researches going on to target some of the different types of leukemias because not only we have CD19 positive leukemia, we have CD22 positive leukemia and many more right? And so, researchers are developing some of those CAR-T cells to target different types of leukemia, not ALL, acute lymphoblastic leukemia, but also acute myeloid leukemia also and also on pediatric side, there are researches going on to target some of the solid tumors, not leukemia but like neuroblastoma or brain tumor. So, those are some of the tumors. They are also developing the CAR-T cells.

26:23.200 --> 26:52.300 <vChagpar> Yeah because it sounds so remarkable that if you can take your own T-cells, re-engineer them such that they can recognize a protein on any cancer cell, if you have a protein on a specific cancer cell and you can force your immune system to recognize that and destroy it, the results that you have had with a single dose of CAR-T therapy with 80% cure rates is really quite remarkable?

26:52.300 --> 28:14.000 <vShah>Yes. So, however, there are different types of the cancers, there are some challenges to face. So, in leukemias, those leukemia cells are floating around in the blood or they are in the bone marrow right, but they are not buried into the tumor. While in some of the solid tumors like neuroblastoma or the brain tumor, the cancer cells are at certain area and some of those cancer cells are buried within the tumor of where therre are some of the other inflammatory cells surrounded right, so for the CAR-T cells to reach and target them directly, it is tough. So, they are now developing the armoured CAR-T cells. So, they have little bit extra arm so that they can go directly to those cancer cells but also can help those some of the surrounding tissue to die out so they can reach those target quickly and kill them also. So, that also is in the frontline, but again it will change in next 5-10 years. I think this CAR-T cell therapy may come little bit on the frontline rather than right now we are using it for the relapse or recurrent diseases only.

28:14.000 --> 29:23.200 <vChagpar> Yeah really exciting stuff. You know, the other question I have to take us back to you know junior high immunology is, you know we think that when cancer cells die or any cells really, that is one of the ways that when your body is getting kind of cleaning up after cells have

died, but that is a way for these antigens to be presented to these T-cells right by the macrophages and so on. It has been a while since, you know junior high immunology folks, so do not quote me on all of the immunology stats, but having said that, do you think that with CAR-T therapy given the fact that you now have introduced this massive immune response, you have killed off these cancer cells, these leukemia cells, so now you have debris, do you think that you have now set up your own immune system, your native T-cells to recognize these antigens, which could provide more long lasting immunity?

29:23.200 --> 29:53.100 <vShah> So that is also being investigated. Right now, whatever is the fact is the direct action between those 2 cells, but those like those debris which are later on recognized by our own cells and then help, that is also in the frontline but nobody has right now analyze that that is also helpful in the long run for the CAR-T patients and there are studies going on in that direction also.

29:53.100 --> 30:25.500 Dr. Niketa Shah is the Director of the Pediatric CAR-T Cell Program at Smilow Cancer Hospital and an Associate Professor of Pediatric Hematology and Oncology at 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 will join us next week to learn more about the fight against cancer here on Connecticut Public Radio.