



Emerging Immunotherapy Treatments for B-Cell Non-Hodgkins Lymphoma

CAR T-Cells.

Dr. Joshua Brody - Hematology/Oncology, Associate Professor, Medicine, Hematology, and Medical Oncology, and Oncological Sciences, Mount Sinai, Director of the Lymphoma Immunotherapy Program, Tisch Cancer Institute

My name is Joshua Brody. I am the Director of the Lymphoma Immunotherapy Program here at the Icahn School of Medicine at Mount Sinai, here in the Tisch Cancer Institute in New York, New York. We get a lot of questions from our patients with all types of lymphomas about the very exciting progress that we've been able to make. And the progress across lymphomas (Hodgkins lymphomas and non-Hodgkins lymphomas) we've been very fortunate (us, our patients, and their families), that the progress has really been unparalleled. We even feel a little guilty sometimes and wish that the progress with other cancers, like pancreas cancer and lung cancer, could've kept pace. But, we've been very fortunate that for lymphomas, the progress of the past decade has been fantastic. We literally have diseases that we used to call incurable, and now we call them partly curable. So, it is gratifying to us, and extremely rewarding to our patients that some of these new therapies can make people live longer, and (as importantly) make people have a good quality of life, and as I say, for some of these diseases, cure patients of their disease. So, hopefully, they may still have to see their doctor at some intervals, but they'll never have to deal with these scary things again. Over the past decade all types of progress, but some of the most exciting progress has been in immunotherapies. And specifically, over the past five years, there are certain types of immunotherapies for non-Hodgkins lymphomas that have been unparalleled i would say in efficacy, and still some of them extremely well tolerated in these things and frequently beloved by our patients because they don't come with some of the toxicities of standard therapies, like chemotherapy or radiation therapy. So, other the past five years, just to focus on non-Hodgkins lymphomas and the subtype we call B-cell non-Hodgkins lymphomas. Lymphoma discussions are always tricky because there are many many types of lymphomas. There are more that 70 types of lymphomas, and sometimes our patients and their families are Googling about lymphomas but they're really not learning about the type that's relevant for them. So, we're gonna focus on, just for the moment, on B-cell non-Hodgkins lymphomas, and this still includes many types, and some of the most common subtypes in there are diffuse large B-cell lymphoma, which we call an intermediary aggressive lymphoma, and some of the lesser aggressive lymphomas we call the low-grade or indolent lymphomas; common examples are follicular lymphoma, marginal cell lymphoma, and SLL CLL. All of them are low-grade in that they do not grow very quickly. In some of the patients with those low-grade lymphomas don't even require any therapy at the time they get diagnosed. For all of these B-cell, not-Hodgkinsons lymphomas, the progress in the past five years regarding immunotherapy has been fantastic in that we we have gotten a couple of specific new therapies that have gotten FDA-approved, and a few that will be FDA-approved over the next year or so that will be very transformative in how we take care of patients. Couple of examples, and perhaps one that have gotten the most press and deservedly so, is this type of immunotherapy called CAR T-cells. CAR T-cells, when I describe this to my patients and their families, they think this is science-fiction, it sounds like it is straight out of Star Trek, but it's a standard therapy that we give everyday. CAR T-cells, the concept is that we take someone's immune cells, a few of them, out of their bodies. It's basically like a long blood draw, most blood draws are for a test, it's a five-minute blood draw. But this is a long blood draw. You have to



actually sit there for an hour giving blood. But you think “I need my blood”. Well, we give you back all the red blood and the parts you need moment to moment, but keep some of the immune cells for the blood draw. The name of this long blood draw is Leukapheresis. We take some of your immune cells using this leukapheresis technique, and we literally ship them off to a factory. The factory used to be in Santa Monica, now there’s a few of them. They take those immune cells and they insert a new gene into those immune cells. That gene is called a CAR, is stands for chimeric antigen receptor. The details aren’t too important, but that CAR gene teaches that immune cell how to recognise lymphoma cells. So now we have the immune cell, the specific name we call that immune cell is a T-cell, so we have a T-cell, we have a CAR gene, we put that CAR into the T-cell, now we call it a CAR T-cell. We take those CAR T-cells, they’re literally sitting in a bag, and we ship them back to the hospital where the patient is waiting. That whole process takes some time, it can take up to three weeks or so, so it’s not an instant or a very simple thing to accomplish. It is a little bit complicated, as you can hear; the leukapheresis, the shipping it out, the manufacture of the CAR T-cell, the shipping it back. And then the CAR T-cells are re-infused back into the patient. For full disclosure, it’s not even quite as simple as that. There is a little bit of chemotherapy given prior to the CAR T-cell re-infusion, but those chemotherapies are fairly gentle compared to some of the other chemotherapies our patients are getting. So, we patients some of this gentle chemotherapy, we re-infuse the CAR-T cells, and it sounds incredibly elegant, and it is incredibly elegant, but there are still some possible risks after the re-infusion of the CAR T-cells. The big risk is that as those immune cells are getting excited to kill lymphoma cells, they can get a little to excited and they can start to spit out chemicals as though they were fighting an infection; there is no infection, it is just the immune cells getting excited because they’ve been programmed to hate these lymphoma cells now. And, when these immune cells get too excited they spit out these chemicals, we call them cytokines, and the consequence of this side effect we call cytokine release syndrome sounds complicated. It’s mostly that patients get a high high fever, and they can get a low blood pressure. This happens to, in a significant degree, to one out of five patients. But, that still, it can be a dangerous thing and therefore we have to keep all the patients in the hospital just to keep a close eye on them for days and days. Patients for this whole process (with the chemo, with the infusion, and the observation), could be in the hospital for ten or eleven days on average. In most patients, they don’t have any of these bad side effects; but some of them do so that’s why we have to keep a close of them. In addition to that high fever, low blood pressure side effect, there is another side effect which is a bit related. Which that during this “immune cells getting all excited while they kill lymphoma”, they can spit out other chemicals which literally make the person get confused. Sometimes we get the patients so confused that they can hallucinate weird or scary things. I literally had a patients, get up, stand up, and start peeing on the wall. I said “what are you doing?”. He said “this is how you do it”. So it can be a very confusing and weird thing that sounds funny, and it can sometimes be weird, but it can also be dangerous, and cephalopathy or neural toxicity associated with CAR T-cells also can happen in a significant degree in one of five patients (not always the patients who get the cytokine release syndrome). So that’s part of the observation as well. So, while this therapy is in many ways very elegant, it still has some real risks; it’s not perfect. And those risks add to the complexity because we need to keep people in the hospital to keep a close eye on them. Nevertheless, the efficacy of these CAR T-cells for all types of these B-cell non-Hodgkins lymphomas, especially diffuse large B-cell lymphoma and follicular lymphoma, and one we didn’t mention before called mantel cell lymphoma, can be, sometimes, well treated with other types of standard chemotherapy. But when those therapies aren’t working, these CAR T-cells are amongst the most effective therapies. The most majority of patients go into remission after CAR T-cell therapy. Not all patients stay in remission, but just from example of this diffuse large B-cell lymphoma, patients who had not have success in prior therapies, we used to call these patients incurable in third-line therapies and beyond. And even in those “incurable” patients, it seems like CAR T-cells are now curing 35 or 40%, four out of ten patients, so that really has been a miraculous revolution in how we take care of those patients. So, remarkable efficacy, pretty good safety compared to other types of chemotherapy; but still not perfectly safe so have to be aware of it.