

CANCER BUZZ: The Promise of Bispecific Antibodies

Originally ran: November 24, 2020

Dr. Firas El Chaer: The cost of the therapies could hopefully drop in the future, especially with the emergence of competition from different companies, different constructs, and different CAR T types, hoping that the cost will, you know, get better in the future. But for now they're definitely expensive. Fortunately, they're covered by insurance companies, by Medicare, for the patients who need them

Host: This time on CANCER BUZZ, CAR T-cell therapy and bispecific antibodies. What you need to know about the future of cancer care is next.

[00:00:40] Welcome to CANCER BUZZ. I'm your host Summer Johnson. On this show, we frequently discuss the latest in developments and promising treatments. Today, we're taking a look at T-cell redirection therapies. There are two main approaches to T-cell redirection that holds significant promise for cancer treatment.

[00:01:00] One is the genetic modification of T-cells with chimeric antigen receptors, also known as CAR T. The other approach is to use bispecific antibodies that can bind to tumor antigens and T-cells simultaneously. CAR T-cell therapies have been very effective in treating B cell malignancies, which has revolutionized cancer immunotherapy. Similar to CAR T, bispecific antibodies have shown promising results in clinical trials.

[00:01:31] In 2014, the FDA approved blinatumomab, the first bispecific T-cell engager, or BiTE, for the treatment of Philadelphia chromosome–negative, relapsed or refractory B-cell precursor acute lymphoblastic leukemia, otherwise known as ALL. In 2017 the FDA expanded that use to all forms of relapsed or refractory B-cell precursor ALL.

[00:01:57] But there are some real challenges for community cancer centers in offering these treatments. The most pressing challenge community programs face are high treatment costs, lack of patient and provider education on these new therapies, and a limited ability to administer select agents.

[00:02:15] Earlier in the show, you heard from Dr. Firas El Chaer. He's an assistant professor at the University of Virginia Emily Couric Clinical Cancer Center. His clinical interests are in leukemias and bone marrow failure syndromes, among others. Dr. El Chaer shared his perspective on the promise of these T-cell redirection therapies and some of the challenges facing their widespread use.

[00:02:40] **Dr. Firas El Chaer:** Let's start first by explaining antibodies, which are basically naturally made in our system against viruses and many other invaders to our system. And, you know, some of these antibodies are made against, as well, cancer cells. However, unfortunately, one of the main reasons cancer cells populate and proliferate that quickly is because our immune system stops seeing them as non-self.

[00:03:03] So basically what happens is it stops recognizing these cancer cells. What we tried to do is basically using antibodies to try to kill these cancer cells. However, we have found out that if we arm these antibodies with special warheads, they are better at killing those cancer cells. And then the next step is using those bispecific antibodies, which is basically—

that's the product's name, it's bispecific—one end of it attaches to the cancer cell and the other end of it attaches to an immune cell, particularly in this case, we're talking about T-lymphocytes, so special types of immune cells.

[00:03:40] And what it does is it gets these immune cells in proximity to the cancer cells and now the immune system can recognize these cancer cells as non-self. Subsequently, the immune cells can release some cytokines and clear molecules that would kill the cancer cells. So basically what we're trying to do is we're trying to retrain the immune system to recognize these cancer cells again, as non-self and subsequently killing them.

Host: [00:04:06] What is the difference between bispecific and CAR T?

Dr. Firas El Chaer: [00:04:10] With bispecific antibodies there's no reengineering of the immune system at all. It's basically, you're just infusing these bispecific antibodies to those patients. And then they attach one end of it to the cancer cells and the other end to the immune cell. And this is how they get all those cells in proximity to each other. In CAR T or chimeric antigen receptor T-cells, there's a whole new reengineering system.

[00:04:35] So from the word, it says “chimera,” which is basically does not exist in nature. So it's manmade. So what happens is the patient's own immune system cells are taken out of the patient—you know, taken to a lab, re-engineered, basically you introduce and you, if you want to put it in basic terms, you introduce a new molecule in those cells that would ultimately be expressed on the surface of these immune cells.

[00:05:00] And then subsequently you would reinfuse it in the patient's body. And this is how the immune cells, which were previously lacking this specific antibody to kill the cancer cells, now they are armed with it, artificially—humans, we armed them. And then now they can subsequently recognize these cancer cells and kill them.

[00:05:20] So overall, it's almost the same mechanism. The only difference is that with the CAR T cells you are reengineering the T-cells and proliferating them in the lab. And this is how they kill the cancer cells. As far as the bispecific antibodies you are not reengineering anything—everything is molecule made in the lab, you're just infusing into the patient's body.

Host: [00:05:40] You work with hematologic diseases. What does the current application of these therapies look like treating those? And then you talked about extending that application to other diseases.

Dr. Firas El Chaer: [00:05:51] So let's talk a little bit about bispecific antibodies. Currently they are approved only as second- and third-line treatment in hematologic diseases.

[00:06:01] As far as I'm aware of, there's only one bispecific antibody currently approved and it's called blinatumomab or BLINCYTO, the brand name, and it is mainly used in acute lymphoblastic leukemia or ALL, which is a very specific subtype of acute leukemia. Bispecific antibodies are currently in clinical trials to be used in other hematologic malignancies, as well as in solid tumors, such as lung cancer, colon cancer, breast cancer, whatever, you name it.

[00:06:30] The struggle that we were having in solid tumors is finding this very specific antigen, which is a protein, on the surface of the cancer cells that can be targeted by these antibodies without actually attacking our own organs that could share these antigens. So this is the main dilemma why these bispecific antibodies are not yet prime in solid tumors, because solid tumors can share a lot of the antigens that we have on our normal human tissue.

[00:07:00] Another reason is whenever we found some of these specific antigens to these solid tumors, the response rates for these bispecific antibodies have been suboptimal so far. However, you know, clinical trials are ongoing, and hopefully in the future we can come up with more specific bispecific antibodies that have better response.

[00:07:21] In the CAR T world, so far they're being tested in hematologic malignancies, not only acute leukemias but in lymphomas as well, and other diseases such as multiple myeloma. We have many clinical trials undergoing in solid tumors, but they are in their infancy right now. So they're not yet commercial available, obviously, but I don't think they will be commercially available for the foreseeable near future.

Host: [00:07:48] What about cost? Is that a challenge as well?

Dr. Firas El Chaer: [00:07:51] Well, that's a broader question for American healthcare system. However, in this particular field, I mean, CAR T therapy is exorbitantly expensive, right? People I'm sure have read many articles in the news whenever the first therapies were first approved. And there were questions about, are these therapies—the cost of them—worth the benefit that they have for the patients' lives?

[00:08:16] Right? I mean, you cannot put a money figure on any human life. However, the cost of these therapies could hopefully drop in the future, especially with the emergence of competition from different companies, different constructs, and different CAR T types, hoping that the cost will get better in the future. But for now they're definitely expensive. Fortunately, they're covered by insurance companies, by Medicare, for the patients who need them.

Summer Johnson: [00:08:43] Can you give us any specific examples of you using these therapies with a patient with ALL.

Dr. Firas El Chaer: [00:08:51] Oh, absolutely. So I was part of the clinical trials that were done on the patients who have ALL or acute lymphoblastic leukemia, who first of all, received CAR T therapy under the clinical trial, before it was approved.

[00:09:03] And obviously now we use it after it was FDA-approved in patients who are younger than 26 years of age. This is the current approval. We're hoping in the future that the approval will expand to all the folks with ALL. I know, CAR T for instance, is approved for, you know, older folks who have lymphoma, which is a different type of cancer or hematological malignancy.

[00:09:23] Bispecific antibodies, they're approved in a much wider age range than ALL. So you can use them in patients who are above age of 18, it's FDA-approved. And, you know, they're approved as single agent as well as part of combination of other chemotherapies.

Host: [00:09:41] That was going to be my next question. Will this take the place of chemotherapy anytime soon?

Dr. Firas El Chaer: [00:09:47] Fantastic question. That's so prime, literally, I think last week or the week before a new paper was published in New England Journal of Medicine, where a very specific subtype of acute lymphoblastic leukemia called Philadelphia positive disease or translocation 9-22. Very subset in acute lymphoblastic leukemia.

[00:10:05] It's more commonly found in older patients who have ALL. You know, the outcomes for this disease historically have been dismal, primarily because once the patient's disease—acute lymphoblastic leukemia—acquires this type of mutation, the prognosis of the disease unfortunately becomes worse. We have been using simplified chemotherapy regimens for those patients, in addition to something called TKI, or tyrosine kinase inhibitors. There's many types of TKIs that are used for this type of disease. The oldest one was called Gleevec, people might have remembered from when it was first covered. It was all over the news and on the cover page of Time magazine, and nowadays we have three generations of TKIs, at least, and many more in the pipeline coming up.

[00:10:54] So even with these TKIs in combination with some form of chemotherapy—the outcomes got better, for sure. But you know, they're not a hundred percent of what we hope for.

Host: [00:11:06] You had an example of very impressive initial outcomes in a study using combination therapy for a particular set of ALL patients. Can you tell us about that?

Dr. Firas El Chaer: [00:11:18] Two weeks ago, a study was presented from Emily [Couric Cancer Center] where patients with acute lymphoblastic leukemia with this particular abnormality—translocation 922, which was Philadelphia chromosome—were treated with prednisone steroids. Then subsequently a TKI. In this case, the sediment was added along with blinatumomab, the BiTE antibody for these patients.

[00:11:43] And outcomes in those patients honestly have been very impressive with the response rate as well as, you know, even with a short follow-up, the survival is definitely much better than historical outcomes in those patients. It was a phase two trial. Currently the FDA here in the United States has not approved blinatumomab in the upfront setting for those patients.

[00:12:07] However, there are many phase three trials ongoing evaluating this type of combination in this patient population, and this is how I see the future for this particular patient population. And this is extremely important because chemotherapy has side effects, and these side effects can affect quality of life, and they have long-term side effects.

[00:12:27] However, having targeted therapy by combining a TKI and blinatumomab, what we have seen is that the early results from morbidity and mortality of this combination and this subset of patient population is extremely low. That is very, very important to consider that when we offer chemotherapy for our patients, you know, it's not only important to get the disease on control or cure them. It's as important to keep a decent quality of life for them.

Host: [00:12:58] Let's talk about the future. What's on the horizon for these therapies? Are there any new clinical trials or new indications or FDA approvals that you know of?

Dr. Firas El Chaer: [00:13:08] So there's a few venues in the future. Number one would just discussed, you know, getting rid of toxic chemotherapy.

[00:13:14] I don't think we're going to be able to get rid of it in all diseases. However, we can at least go down from, let's say, a combination of five drugs to the combination of two drugs whenever we have the chance to add a targeted therapy, such as blinatumomab or BiTE or CAR T. Another thing is—the future in the field of hematologic malignancy is something called MRD or measurable residual disease, previously known as minimal residual disease. And this is basically the tiniest level of, in our case, leukemia that could be detected in those patients. We know that the lower this MRD, which means that MRD-negative disease, the patients do much better long-term as far as survival and outcomes than when compared to patients who have MRD-positive disease. Even if these BiTEs or these CAR T-cells are not used to debulk the disease in the upfront setting, their job, I think in the future, can definitely be to get rid of this MRD positivity, therefore offering longer survival and better outcome for those patients.

[00:14:21] Number three, as we're learning so much more about the immune system. So unfortunately, these therapies, they do work, but they don't work all the time. And when they work in many instances, they stopped working after a while. Cancer cells are very smart that they overcome the benefit of these therapies by developing resistance.

[00:14:40] So we're learning how to overcome this resistance by combining other type of immunomodulators or immunotherapies that could potentially, you know, overcome, reverse the resistance to these therapies.

Host: [00:14:53] I read somewhere that you think this is the most important trend in cancer care. What do oncology teams need to know about these therapies?

Dr. Firas El Chaer: [00:15:03] So I get this question a lot, because you know, when these therapies are presented, they're presented—or we'll call it polished. So yes, they are not cytotoxic chemotherapy. However, they still come with side effects. Particularly one of them is called CRS, or cytokine release syndrome, which in many instances, particularly in CAR T much more than BiTE, require intensive care unit admission and have, you know, an associated mortality, not only morbidity.

[00:15:33] So for CAR T and less likely for bispecific, I see it's going to be a long time before it gets adopted by community oncologist or the community cancer centers. However, there are many startups that are trying to attach that, or those modules, in community centers.

Host: [00:15:56] You can find more information and resources on CAR T therapies and bispecific antibodies in the show notes. Thank you for supporting CANCER BUZZ. If you're enjoying the show, please leave us a review on Apple Podcasts and share the episode with a colleague. That allows us to continue to provide you with the latest news and resources in cancer care.

[00:16:35] Until next time, for the entire CANCER BUZZ team, I'm Summer Johnson.