What is the best lymphoma treatment after CAR T therapy fails?

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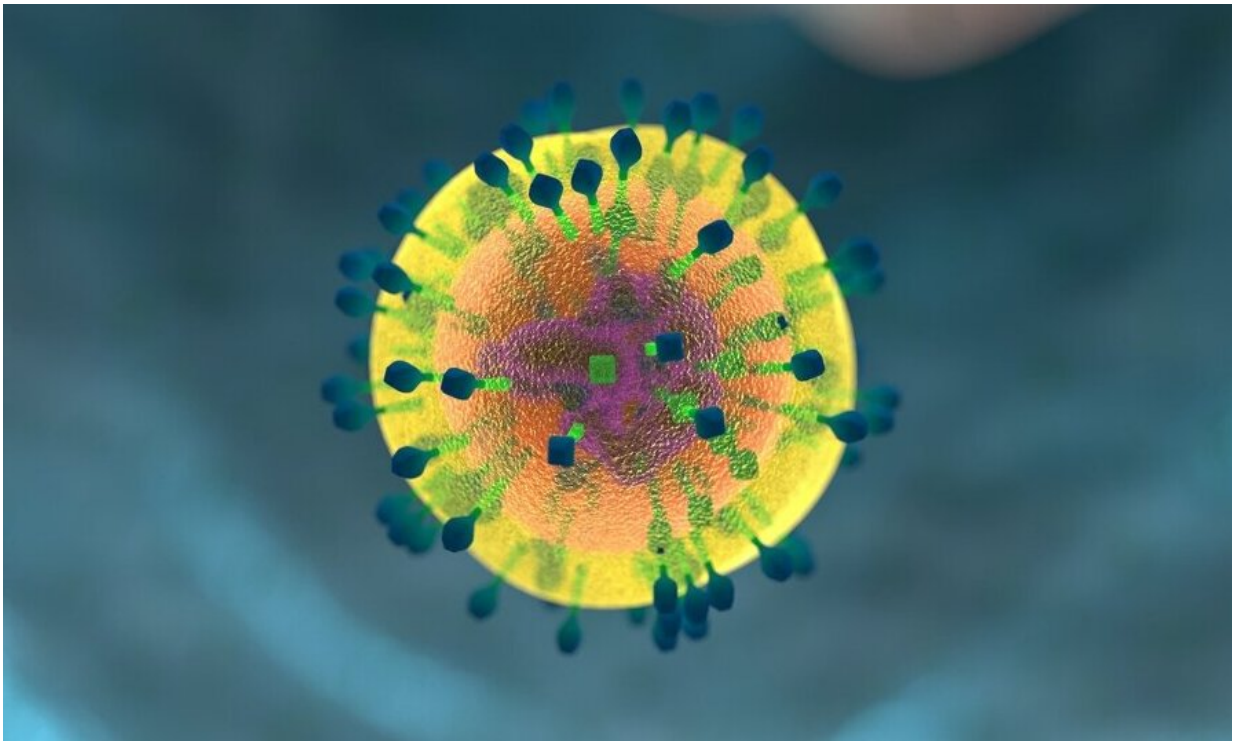

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For 30% to 40% of lymphoma patients who receive CAR T therapy, the treatment is a godsend. Typically given to lymphoma patients for whom other treatments have proven ineffective, CAR T therapy involves removing immune cells from the body via a blood draw, reengineering them to become better cancer fighters, then reintroducing them to the

bloodstream, where they seek out and destroy cancer cells.

For 60% to 70% of lymphoma patients who receive CAR T therapy, however, the treatment doesn't work, and the cancer comes back—typically within a year after treatment. Cancer researchers have started looking into additional treatments for lymphoma patients who relapse after CAR T therapy—one thought being that drugs called checkpoint inhibitors, which prevent proteins in the body from inhibiting the immune system, could be a method for reinvigorating the reengineered immune cells.

University of Colorado Cancer Center member Ajay Major, MD, MBA, assistant professor in the division of hematology in the CU School of Medicine, recently published research in the journal *Blood Advances* that shows checkpoint inhibitors are not an effective treatment when CAR T fails; he is also interested in the potential of new medications called bispecific antibodies to treat aggressive lymphomas.

We talked with Major about his research.

How did this research get started?

This was a project I started working on during my fellowship at the University of Chicago. We were struggling with this exact problem: When people relapse after CAR T, how do we help them? My mentor at the University of Chicago, Justin Kline, MD, has done a lot of research on the tumor microenvironment, or how the immune system affects the CAR T cells, as well the tumor cells themselves. There was some initial research that showed we could potentially rejuvenate CAR T cells by giving these checkpoint inhibitor therapies that act on PD-1 and PD-L1 proteins.

How exactly do the checkpoint inhibitors work to rejuvenate the CAR T cells?

PD-1 and PD-L1 are proteins in the body that are considered inhibitory, which means that they basically "turn down" the immune system. This is seen in a lot of cancer types. What some research found is that in patients who had relapsed, aggressive lymphomas after CAR T therapy, when you looked at their tumors again, not only the CAR T cells, but also the cells in the tumor had high levels of PD-1 and PD-L1. We already have checkpoint inhibitor drugs that block those inhibitory proteins, so the idea is, could we prevent that inhibition that's happening in the immune system and potentially allow the CAR T cells to expand and become active again?

What questions were you looking to answer with your research?

One of the reasons we think that CAR T stops working is that the CAR T cells become exhausted. So researchers have been looking at ways to rejuvenate those cells, or "refuel the CAR." There was some initial research that showed that checkpoint inhibitors might be a way to do that, but no one had studied a large group of patients. There were smaller studies that had been done. Dr. Kline and I said, "We should probably get together as many patients as we can, in a multicenter study, and see what is really happening."

How much data did you look at for this study?

We were able to collect data on 96 patients from 15 centers, thanks in large part to CU Cancer Center members Brad Haverkos, MD, and Manali Kamdar, MD, who provided many patient cases to this study. This isn't a super-common scenario, so we wanted to gather as many

patients as possible. We also wanted to see how this strategy works in the real world, rather than a clinical trial setting where you get to select patients.

What were your findings?

What we found is that this strategy of using checkpoint inhibitors after CAR T fails doesn't appear to be very effective for most patients. Only 19% of patients had a response to checkpoint inhibitor therapy, and only 10% had a complete response. The amount of time that people were alive without progression of the disease—also known as progression-free survival—is only 54 days, and the average survival was only 159 days.

Was that in line with what you were expecting?

While we were putting together the study, I talked to many colleagues who treat lymphoma. Most of them agreed that these numbers lined up with their anecdotal experiences treating these patients. Only 5% of patients in this study had long-term remissions just from the checkpoint inhibitor. Overall, the strategy doesn't seem to be working in most patients.

Was the goal of your research to eliminate checkpoint inhibitors as a strategy in this situation?

What we were attempting to do was to see if this really works in the real world. And if it does, are there specific groups of patients for whom this strategy might work? One of the things we found is that patients with certain types of lymphoma, specifically primary mediastinal B cell lymphoma, and also patients who had a later relapse after CAR T—people who had relapsed six months or later after they receive CAR T—had better responses to this strategy.

What do you want people to take away from your research?

There has been a lot of research put into this space, and we wanted to find out if this is really the right strategy to pursue for patients. We know that some of the bispecific antibody therapies and other targeted agents that are coming out work well on aggressive lymphomas after CAR T has stopped working. That's what we have to think about—if CAR T doesn't work for everyone, we need to come up with better strategies for which treatments have the best effectiveness. At this point, the checkpoint inhibitors, except for a very select amount of patients, don't seem to be that effective. I think we should be putting our resources into some of these other agents that we know are more effective, and our vision in the lymphoma program is to open new clinical trials and develop new therapeutic approaches targeting this clearly unmet need for our patients.

More information: Ajay Major et al, Efficacy of checkpoint inhibition after CAR-T failure in aggressive B-cell lymphomas: Outcomes from 15 U.S. institutions, *Blood Advances* (2023). DOI: 10.1182/bloodadvances.2023010016

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