mRNA Cancer Vaccine May Boost CAR-T Response

A vaccine designed to enhance T-cell activity could help CAR-T therapy work better against solid tumors.

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The same messenger RNA (mRNA) technology used for COVID-19 vaccines may help improve response to CAR-T immunotherapy for solid tumors, according to research presented at the American Association for Cancer Research Annual Meeting (AACR 2022) this week in New Orleans.

Chimeric antigen receptor T-cell therapy—better known as CAR-T—is a "living drug" that reprograms a patient's own T cells to fight cancer. The treatment involves removing a sample of a patient's white blood cells, genetically modifying T cells to express a synthetic receptor that recognizes their cancer, manufacturing a large number of the modified cells and infusing them back into the body. CAR-T therapy is highly effective for certain blood cancers, but it does not work well against solid tumors.

John Haanen, MD, PhD, of the Netherlands Cancer Institute in Amsterdam, and colleagues, in collaboration with Ugur Sahin's team at BioNTech in Germany, tested a novel type of CAR-T therapy that targets claudin-6 (CLDN6), a tumor-specific antigen that is widely expressed on multiple types of solid tumors but usually not in healthy adult tissues.

"One of the main limitations [of CAR-T therapy] is that most of the proteins present on solid tumors that could be used as targets are also found at low levels on normal cells, making it difficult to specifically direct the CAR T cells against tumor cells and spare healthy ones," Haanen explained in an AACR press release. "Other challenges include the limited persistence of CAR T cells observed in solid tumors and their difficulty reaching the tumors and penetrating the center of the mass."

To overcome these challenges, Haanen and colleagues tested CLDN6 CAR T cells alone and in combination with an mRNA vaccine, dubbed CARVac, designed to amplify T-cell expansion and activity.

The mRNA vaccine approach uses lipid nanoparticles, or fat bubbles, to deliver bits of genetic material that encode instructions for making proteins. For example, the Pfizer-BioNTech and Moderna COVID-19 vaccines deliver blueprints for making the SARS-CoV-2 spike protein. When the

vaccine is injected into a muscle, the cells produce the protein, triggering an immune response against the virus.

CARVac delivers instructions for making CLDN6. The vaccine is taken up by immune system dendritic cells, which then express the protein on their surface. BioNTech researchers previously reported that the combination treatment, known as BNT211, led to greater proliferation, persistence and functionality of CLDN6-directed CAR T cells in mice.

Haanen and colleagues evaluated this approach in a Phase I/II clinical trial (NCT04503278) that enrolled people with advanced CLDN6-positive solid tumors that did not respond to or relapsed after prior therapy (eight with testicular cancer, four with ovarian cancer and four with various other tumor types).

In the first part of the study, participants were treated with escalating single doses of CLDN6 CAR T cells alone. In the second part, patients received CAR T cells plus the CARVac vaccine, administered every two to three weeks for up to 100 days after the CAR-T infusion, followed by maintenances doses every six weeks. Prior to infusion of the modified cells, the participants received strong conditioning chemotherapy to kill off their existing T cells and make room for the new ones; however, some testicular cancer patients who had already received high-dose chemotherapy and undergone stem cell transplants received a milder conditioning regimen.

All 16 treated participants experienced “robust” engraftment of the modified T cells, Haanen reported. At six weeks after the CAR-T infusion, six of the 14 evaluable patients (four with testicular cancer and two with ovarian cancer) experienced partial tumor remission, for an overall response rate of 43%. Six additional participants had stable disease without further progression, resulting in a disease control rate of 86%. At 12 weeks after the CAR-T infusion, four of the six partial responders had deepening responses, but some others experienced disease progression. One testicular cancer patient had a complete response that was still ongoing six months post-infusion. People treated with the higher dose of CAR T cells had better outcomes, and those who received CAR T cells plus the vaccine had an overall response rate of 80% (four out of five patients).

Commenting on the presentation, Vincent Lam, MD, of Johns Hopkins University, who was not involved in the study, suggested that CAR T persistence does not appear to be consistently enhanced yet, but optimizing the CAR-T dose or the timing or duration of the vaccine might improve effectiveness.

The treatment was generally safe, with the expected CAR-T side effects. Unleashing modified T cells can trigger a potentially life-threatening immune reaction known as cytokine release syndrome (CRS), which can lead to a drop in blood pressure, organ failure and neurologic toxicity. About half of the study participants experienced manageable CRS, and one had mild neurotoxicity. Patients who received the vaccine had transient flu-like symptoms. Other adverse events included temporary low blood cell counts and impaired immune response. Some patients had elevated lipase levels, a possible sign of pancreatic toxicity. Severe side effects were more common at the

higher dose level.

“The infusion of CLDN6 CAR T, alone or in combination with CARVac, is safe and holds promise for patients with CLDN6-positive cancers,” Haanen said. “CLDN6 was never targeted before with cellular therapy, but in our study, this approach is already showing efficacy that may be better than the data from other CAR T trials in solid tumors.”

“The results support our assumption that claudin-6 is a well-suited new tumor target,” BioNTech chief medical officer Özlem Türeci, MD, said in a press release. “Bringing these innovations together in one regimen may benefit patients with hard-to-treat solid tumors with an otherwise poor prognosis, such as advanced testicular cancer. Our preliminary data indicate that the successes of CAR-T in hematological cancers may indeed be transferred to solid tumors.”

BNT211 is just one of more than a dozen mRNA therapies BioNTech is developing for cancer, according to BioSpace. Moderna is also studying several mRNA vaccines for cancer treatment.

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