ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Chimeric Antigen Receptor T-Cell Therapy Plus Checkpoint Blockade in Thoracic Cancers

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H&O How has immunotherapy impacted outcome in thoracic cancers?

PA In the past 5 years, knowledge of immunology in thoracic cancers has greatly improved. The results observed with immunotherapy are encouraging. For example, in patients with stage 4 non–small cell lung cancer, 5-year survival was previously 2%. That survival rate has now increased to approximately 20% with the use of checkpoint blockade immunotherapy. Similarly, early data from our trial combining chimeric antigen receptor (CAR) T-cell therapy and checkpoint blockade in mesothelioma were promising. In a recent multicenter trial evaluating combination immunotherapy with anti–programmed death 1 (PD-1) and anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) agents, the overall survival improved, even in patients with biphasic and sarcomatoid subtypes of mesothelioma.

Based on preclinical data, ongoing trials are now investigating the combination of chemotherapy and immunotherapy, and further moving the immunotherapy to earlier stages of disease. Studies of patients' tumors indicate that with higher immune responses in early-stage thoracic cancers, there is a survival benefit. Ongoing induction and adjuvant trials will hopefully further improve outcomes in thoracic cancers.

H&O What did your study of CAR T-cell therapy in thoracic cancers show?

PA When evaluating high-risk novel therapies, the first objective is to show that they are safe. In our study, CAR T cells were injected directly into the patient's chest cavity, and there was much concern about the safety. We showed, in more than 40 patients, that this route of administration is safe. The toxicity profile was also safe. In hematologic malignancies, CAR T-cell therapy is associated with cytokine-release syndrome and neurotoxicity. These adverse events have not been seen in solid tumors.

Patients with pleural mesothelioma or metastatic lung or breast cancer were eligible for the trial. We administered increasing doses of CAR T cells, by cohort, directly into the pleural cavity. In the later half of the study, based on our published preclinical data, we administered anti–PD-1 antibodies to patients who received intrapleural CAR T cells. We observed that this combination immunotherapy approach was safe and showed evidence of antitumor efficacy.

Our preclinical study confirmed that injection of the CAR T-cell therapy directly into the pleural cavity provides immunologic benefits not seen with intravenous administration. The preliminary results of our clinical trial validate the preclinical results. Another important

observation is that although we targeted one specific cancer-cell surface antigen, a wider immune response was seen, a phenomenon known as epitope spreading. It has been shown in immunotherapy studies that epitope spreading can help expand immune responses, resulting in improved antitumor efficacy.

Our data showed that this treatment is safe, that pleural administration is highly feasible, and that the addition of checkpoint blockade can prolong CAR T-cell persistence. These therapeutic approaches could be advantageous when they are combined in a safe, rationale-based manner. We hope that future trials will confirm this observation, and extend survival.

H&O Do CAR T-cell therapies for thoracic cancers differ from those used in hematologic malignancies?

PA These settings are very different. For example, hematologic malignancies are distributed throughout the body, including the bone marrow, and have ready access to T cells. In contrast, solid tumors can mount a fortress of immunosuppression and prevent T cells from entering the tumor. The first CAR T-cell therapies approved in hematologic malignancies targeted the CD19 antigen. CD19 was an ideal candidate antigen that is homogeneously expressed on target cancer cells. CD19-targeted CAR T-cell therapies are associated with good efficacy and tolerable safety. Solid tumors, however, are heterogeneous not only in terms of antigens, but also the immune environment.

In addition to the above mentioned factors, tumoral stroma, lymph nodes, immunosuppressive macrophages, and regulatory T cells all influence the efficacy of CAR T-cell therapy. Ongoing research is investigating how to modulate the solid tumor microenvironment, which is rich in these factors, to improve CAR T-cell therapy efficacy.

H&O Are there strategies to enhance the function of CAR T-cell therapy?

PA In our trial, we combined CAR T-cell therapy with checkpoint blockade therapy. This regimen is now in phase 2 trials. However, anti–PD-1 therapy is often administered indefinitely. To avoid this need, we genetically engineered the CAR to carry a decoy receptor, known as the PD-1 dominant negative receptor (PD-1 DNR). As a decoy receptor, PD-1 DNR can bind to programmed death ligands 1 and 2, which are expressed on the cancer cell surface, to prevent the CAR T cells from becoming exhausted.

Based on preclinical data supporting strong antitumor efficacy of CAR T cells with PD-1 DNR, we designed a phase 1 clinical trial that was approved by the US Food and Drug Administration. We are now recruiting patients for this trial. We hope that the study will provide a signal that it is possible to genetically engineer a CAR T-cell therapy to accomplish multiple functions, and that the approach can be extended to multiple solid tumors. Targeting one antigen with one strategy may not eradicate the disease. Combining strategies and using the T cells as a delivery vehicle to bring them to the tumor is probably more beneficial.

Researchers are also investigating similar approaches that counteract transforming growth factor beta, increase the functional memory of the cells infused, and overcome the stromal microphages. All of these approaches have shown benefit in preclinical studies. The way to safely combine these approaches and effectively deliver them to the tumor, in my view, is through the T cell.

H&O Are there barriers to the use of CAR T-cell therapy in thoracic cancers?

PA There are several barriers, but I am hopeful that they will be overcome as the data accumulate. Typically, the phase 1 studies enroll patients with stage 4 cancer who do not respond to chemotherapy and prior immunotherapy. Patients with these advanced solid tumors have profound immunosuppression. We are now trying to move immunotherapy to earlier stages. Once we have initial safety data, it may be possible to move cell therapies to early-stage cancers. As has been seen in other settings, even in solid tumors, the earlier we can build up an immune response, the more likely the patient will benefit.

Furthermore, patients with early-stage cancer can undergo resection of the tumor to provide insight into the impact of treatment. It may be possible to build strong systemic immune responses to prevent cancer recurrence in earlier stages, rather than waiting to treat at late stages.

H&O Can use of CAR T-cell therapy in hematologic malignancies provide insight into use in thoracic cancers?

PA When we started this research, I learned a tremendous amount from working next to hematologic oncologists. For example, the single-chain variable fragment that was used to build the first CARs was uniformly derived from a mouse monoclonal antibody. These agents are effective at first, but after a while, patients build up antibodies against the mouse component, and the CAR T cells do not persist. We are among the first researchers to make fully human CARs, which contributed to long-term persistence.

Clinicians in hematology/oncology also provided a strategy for the management of toxicities, such as

cytokine-release syndrome and neurotoxicity. The cell therapy nursing team had already streamlined the care management process, including cell infusion, monitoring, and follow-up, so there was an existing platform that we could use in patients with solid tumors. We were able to avoid mistakes by learning from their experience. It was educational to discuss the cases and any complications with my colleagues in hematology.

> It is now known that with genetic engineering, it is possible to incorporate multiple functional strategies within a single CAR.

H&O Do you have any recommendations regarding the use of CAR T-cell therapies in thoracic cancers?

PA I have 3 main recommendations. First, after safety is confirmed, CAR T-cell therapy should be evaluated in early-stage cancers. Second, the clinical readout must improve. With chemotherapy, imaging scans are used to assess the response. We now know that a response to immunotherapy takes time to manifest. A key indicator that treatment is successful is when the patient begins to feel well and is able to retain weight. In the setting of immunotherapy, scans are misleading. A scan might indicate progression in a patient who is in fact responding to treatment. A better clinical readout might incorporate biomarkers. Third, I would recommend that solid tumor oncologists work collaboratively with cell therapy physicians and hematologic oncologists to rapidly translate therapies in an efficient manner.

H&O Will the role of CAR T-cell therapies in thoracic cancers evolve?

PA There are currently ongoing studies of T-cell therapy in thoracic cancers, but they are in early stages. The role of CAR T-cell therapies, particularly in combination regimens, will evolve. CAR T cells are a good delivery vehicle. Research has shown that CAR T-cell therapy can target an antigen and deliver treatment to the tumor. It is now known that with genetic engineering, it is possible to incorporate multiple functional strategies within a single CAR. A combination of these attributes will allow the use of CAR T-cell therapies to evolve with increased clinical benefit in the next few years.

Disclosure

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Suggested Readings

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