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MD Anderson researchers present cellular therapy advances at the 2022 ASCO Annual Meeting

Highlights include three-year data from ZUMA-2, gamma delta CAR T cell therapy and NK cell combination treatment

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ABSTRACTS 7518, 7509, 8009

CHICAGO — Promising clinical results with cellular therapies for patients with blood cancers highlight advances being presented by researchers from The University of Texas MD Anderson Cancer Center at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting.

These findings include long-term outcomes of patients receiving an infusion of brexucabtagene autoleucel (KTE-X19) for mantle cell lymphoma, efficacy of gamma delta CAR T therapy for aggressive B-cell lymphoma and responses of umbilical cord blood-derived expanded natural killer cells when given together with combination therapy before stem cell transplant.

CAR T cell therapy shows durable responses after three years for patients with mantle cell lymphoma (Abstract 7518)

Three-year follow-up data from the Phase II ZUMA-2 trial showed a long-term survival benefit and low disease relapse potential with one infusion of the anti-CD19 chimeric antigen receptor (CAR) T cell therapy brexucabtagene autoleucel (KTE-X19) in patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL). Principal investigator Michael Wang, M.D., professor of Lymphoma and Myeloma, presented results from the trial, and study results were published in the *Journal of Clinical Oncology*.

The updated results include all 68 patients treated with KTE-X19 on the trial with an additional two years of follow-up. After 35.6 months median follow-up, the overall response rate was 91%, with a 68% complete response rate. The median duration of response was 28.2 months, with 25 of 68 treated patients still in ongoing response at data cutoff.

“This represents the longest follow-up of CAR T cell therapy in patients with mantle cell lymphoma to date,” Wang said. “It is encouraging to see this therapy induced durable long-term responses and a low relapse rate for these patients.”

All patients had R/R disease after receiving up to five therapies, and all had received previous Bruton’s tyrosine kinase (BTK) inhibitor therapy. BTK inhibitors have greatly improved outcomes

in R/R MCL, yet patients who have subsequent disease progression are likely to have poor outcomes, with median overall survival of just six to 10 months. Few patients in this category qualify to proceed to an allogeneic stem cell transplant.

Response and survival benefits were positive regardless of the prior BTK inhibitor type. Ongoing effectiveness trended lower in patients with prior acalabrutinib exposure. More investigation is needed to determine the mechanism behind these differences. The findings support future study of CD19-directed CAR T cell therapy in patients with high-risk MCL in earlier treatment lines.

The researchers also evaluated minimal residual disease (MRD) as an exploratory endpoint using next-generation sequencing on 29 patients. Of those, 24 were MRD-negative at one month, and 15 of 19 with available data were MRD-negative at six months. Circulating tumor DNA analysis of MRD at three and six months was predictive of disease relapse.

The treatment was well tolerated, as reported in previous studies with this therapy. Only 3% of treatment-emergent adverse events (AE) of interest occurred since the primary report. The most frequent Grade ≥3 AE was neutropenia.

The study was funded by Kite Pharma, a Gilead Company. Wang has received research support and has served on the advisory board and as a consultant for Kite Pharma. A complete list of collaborating authors can be found within the abstract here.

Allogeneic gamma delta CAR T cell therapy displayed encouraging efficacy in B-cell lymphoma (Abstract 7509)

In the Phase 1 GLEAN trial of ADI-001, an anti-CD20 CAR-engineered allogeneic gamma delta T cell product, the treatment was well tolerated and showed continued efficacy in patients with R/R aggressive B-cell lymphoma. Results from the ongoing trial were presented by Sattva Neelapu, M.D., professor of Lymphoma and Myeloma.

The first-in-human trial enrolled ten patients and eight were evaluable and monitored for at least 28 days. The median age was 62 years and patients received a median of 4 prior therapies. At Day 28, the overall response rate (ORR) and complete response (CR) rate based upon PET/CT was 75%. The ORR and CR rate was 80% at dose levels two and three combined. The ORR and CR rate in CAR-T relapsed patients was 100%.

“The responses to ADI-001 in this population of heavily pre-treated and refractory lymphoma patients, including in those with prior CD19 CAR T cell therapy, is very promising,” Neelapu said. “These results suggest the potential for off-the-shelf gamma delta CAR T cell therapy to be an effective treatment possibility for patients with B-cell lymphoma.”

While autologous CD19-targeted CAR T cell therapy has been effective in R/R large B-cell lymphoma, there remains a need for alternative cell-based therapies. This study uses a subset of T cells, known as gamma delta 1 T cells, isolated from the peripheral blood of donors as the basis for CAR T cell therapy.

Gamma delta 1 T cells are desirable because they are able to combine both innate and adaptive mechanisms to recognize and kill malignant cells, and high levels of these cells in hematologic and solid tumors are associated with improved clinical outcomes. ADI-001 expresses major histocompatibility complex (MHC)-independent gamma delta T cell receptors, therefore lowering the risk of graft versus host disease (GvHD) without the need for gene editing.

The median age on the study was 62 years, and patients had received a median of 4 prior therapies. The treatment was well tolerated with most related events being grade 1 or 2. There were two cases of cytokine release syndrome and one case of immune effector cell-associated neurotoxicity syndrome. There were no reported cases of GvHD or dose-limiting toxicity.

Enrollment in the trial is ongoing and a potentially pivotal program is planned.

The study was funded by Adicet Bio, Inc. Neelapu has received research support and has served on the advisory board and as a consultant for Adicet Bio and has intellectual property related to cell therapy. A complete list of collaborating authors can be found within the abstract here.

Expanded NK cells combined with chemoimmunotherapy achieved durable responses in multiple myeloma (Abstract 8009)

Results from the expansion phase of a Phase II clinical trial demonstrated that umbilical cord blood-derived expanded natural killer (NK) cells combined with chemotherapy and immunotherapies achieved durable responses in patients with multiple myeloma. Results from the completed clinical trial were presented by Samer Srour M.D., assistant professor of Stem Cell Transplantation & Cellular Therapy.

Thirty patients on the trial received NK cells plus elotuzumab (an immunotherapy monoclonal antibody), lenalidomide (an immunomodulatory drug) and high-dose melphalan chemotherapy before autologous stem cell transplant (ASCT).

At three months post-transplant, 97% of patients achieved at least a very good partial response (VGPR), including 76% with a complete response or stringent complete response, while 75% were minimal residual disease (MRD)-negative. At a median follow-up of 26 months, only four patients had progressed. At two years, the progression-free survival rate was 83% and the overall survival rate was 97%.

“Patients with high-risk multiple myeloma have more options to treat their disease than previous years, but they continue to have poor outcomes,” Srour said. “These results indicate excellent hematologic and minimal residual disease responses and improved survival for these patients, suggesting this approach could provide an additional treatment opportunity.”

NK cells are white blood cells that monitor the body for virus-infected and cancerous cells. MD Anderson researchers pioneered the approach to isolate and expand NK cells from umbilical cord blood to be used as cellular therapies. Lenalidomide enhances NK cell function and antibody-mediated cell toxicity against tumor targets. Preclinical data showed that lab-expanded NK cells demonstrated higher elotuzumab-mediated cytotoxicity against myeloma targets than non-expanded cells, and that the addition of elotuzumab to lenalidomide amplified the cord blood-NK cell antibody-dependent cellular cytotoxicity against a commonly used cell line to evaluate novel therapies for multiple myeloma (MM1.S) targets.

The study enrolled 30 patients with high-risk multiple myeloma, with a median age of 63. Twenty-nine patients (97%) had Revised Multiple Myeloma International Staging System (R-ISS) stages 2/3, 40% had ≥2 high-risk genetic abnormalities, and 23% had deletions or mutations of *TP53*. The primary endpoints were best response rate (≥VGPR) and MRD three months after ASCT.

Before the ASCT, stem cells are taken from the patient and stored. After treatment with the immunotherapy and chemotherapy drugs, stem cells are then returned to the patient to replace the blood-forming cells that were destroyed by the chemotherapy.

The treatment was well tolerated, with no unexpected serious adverse effects attributable to NK cells noted. The investigators plan to launch a randomized clinical trial to further explore this treatment combination for patients with high-risk multiple myeloma.

This study was supported with funding from the High-Risk Multiple Myeloma Moon Shot®, part of MD Anderson's Moon Shots Program®, a collaborative effort to accelerate the development of scientific discoveries into clinical advances that save patients' lives. The research also was supported by Celgene, a Bristol Myers Squibb company.

Srour has no conflicts of interest. A complete list of collaborating authors can be found within the abstract here.

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