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Researchers compose guidelines for handling CAR T cell side effects

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Immune-cell based therapies opening a new frontier for cancer treatment carry unique, potentially lethal side effects that provide a new challenge for oncologists, one addressed by a team led by clinicians at The University of Texas MD Anderson Cancer Center with proposed guidelines for systematically dealing with the toxicities of these drugs.

Their work, published today in *Nature Reviews Clinical Oncology*, confronts the two main side effects of chimeric antigen receptor T-cells, known as CAR T cells, white blood cells genetically engineered to strike cells with a specific target on their surface.

"CAR T cells provide an entirely new level of improved disease response among patients with certain blood cancers and hold promise for more wide-ranging use," said Elizabeth Shpall, M.D., deputy chair and professor of Stem Cell Transplantation and Cellular Therapy at MD Anderson.

"The algorithms that we published are conservative, detailed, and will help us save lives as we move forward with these exciting but also more toxic therapies," Shpall said.

The review covers wide-ranging research on CAR T therapies by many institutions and includes insights based on more than 100 patients treated at MD Anderson, Moffitt Cancer Center in Tampa, Sylvester Cancer Center at the University of Miami, and Mayo Clinic Cancer Center in Rochester, Minn.

Patients were treated by the co-authors with CAR T cells under development at four different companies for leukemias and lymphomas that attack white blood cells called B cells. They target CD19, a protein found on the surface of both malignant and normal B cells.

In clinical trials of CAR T for patients who have had all other treatments fail, response rates range from 50 to 90 percent.

"This represents a sea change in how we treat these patients," said lead author Sattva Neelapu, M.D., professor of Lymphoma and Multiple Myeloma. "There have been no new treatments approved for patients with aggressive B-cell lymphomas relapsing after first line therapy in 30 years, and only about 10 percent survive long term."

"Existing second-line treatments, combination chemotherapy followed by autologous stem cell transplant when possible, take three to six months," Neelapu continued, "CAR T cell therapies take a few weeks."

"We need longer term follow up of patients treated so far in clinical trials, but these are potentially curative treatments," Neelapu said. "The toxicities are unique, and every member of the care team needs to be trained to recognize them and act accordingly."

Cytokine storms, brain stressors and safety

Two side effects have emerged during clinical trials that were previously uncommon to cancer treatments:

- Cytokine release syndrome (CRS), also known as cytokine storm, an escalated immune response that causes flu-like symptoms and can be fatal.
- Neurological toxicity that the researchers have named CAR-T-cell-related encephalopathy syndrome (CRES), which can

sometimes lead to lethal swelling in the brain.

Both CRS and CRES are treatable, with early identification important to swift improvement.The review provides specific recommendations for pre-treatment preparation, monitoring of patients during and after CAR T infusion, identifying and staging emerging CRS and CRES, and tailored treatment of those side effects depending upon their severity.

New test for neurotoxicity

Researchers also developed a simple and fast method to flag development of neurotoxicity. The 10-point test asks a patient to name the year, month, city, hospital and president/prime minister of their home country (5 points), to name three nearby objects (3 points), write a standard sentence and count backward from 100 by tens.

A perfect score defines normal cognitive function. A patient has mild to severe impairment depending on the number of questions or activities missed.

For one patient treated for B cell lymphoma cited in the review, deterioration of her handwriting was the first sign of neurological impairment, which led to prompt intervention and reversal of the toxicity within hours.

Building on such insights, co-lead author Sudhakar Tummala, M.D., professor of Neuro-Oncology, led development of the neurological assessment, which they named CARTOX-10. An existing general method didn't effectively quantify the neurological effects caused by CAR T cell therapies.

They also tap the existing research published or presented about these therapies. For example, CAR T cell pioneer Carl June, M.D., and

colleagues at the University of Pennsylvania, found abundant expression of interleukin-6 to be a driver of cytokine release syndrome. They successfully treated the first pediatric patient who suffered from CRS with IL-6 suppressors.

The review provides detailed guidance on how and when to use such drugs and other therapies for CRS and CRES.

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