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Press release

Research

A New Framework for Understanding and Tackling CAR T Toxicities

Immunotherapy using CAR T cells is finding ever more applications. In addition to their use in the treatment of blood and lymphatic cancers, CAR T-cells are now also being investigated for solid tumors and various autoimmune diseases. With the growing number of indications and patients, the issue of side effects associated with this innovative therapy is becoming even more pressing. A team led by Privatdozent Dr. Kai Rejeski from the Department of Medicine III at the LMU University Hospital Munich has proposed a new strategy in the renowned journal *Nature Medicine* to systematically and more rapidly address novel and emerging side effects. The strategy is called IAGO – like the villain in Shakespeare's *Othello*.

As more patients survive for many years thanks to CAR T-cell therapy, long-term side effects in the survivorship phase are increasingly coming into focus. Examples include inflammation of the nervous system, prolonged changes in blood counts, and secondary tumors – but especially, and on a large scale, infections. "This is because CAR T-cells remain in the body as a "living drug" and continue targeting the patients immune cells, namely B cells, which ultimately leads to an antibody deficiency," says Rejeski. "In addition, persistent cytopenias and long-term suppression of the body's own T-cells – for example, due to the initially applied lymphodepleting chemotherapy – can weaken the immune system in the long run."

"That's why," the physician and research group leader continues, "infections must not be downplayed. They can occur frequently and be severe, and this must be kept in mind if we want to optimize outcomes for our patients." To systematically detect and treat them in the best possible way, research at university hospitals is required. And research at university hospitals requires structured data collection, including close collaboration with community-based physicians who provide long-term care for patients.

Better reporting systems for CAR T associated infections needed

"In this sense, we need new reporting systems with defined standards for

CAR T associated infections," says Rejeski. Standards that answer questions such as: When did the infection occur – within the first 30 days or later? Was it bacterial, viral, or fungal? How severe was it? Did it occur while the patient was in the hospital or at home? Was the patient on antibiotic prophylaxis when the infection developed?

"These are all key pieces of information we need in order to truly compare the infection risks of different CAR T products using the same uniform criteria. And here," Rejeski adds, "we urgently need to improve."

Structured data collection as a basis for better treatment

This is where IAGO comes in. IAGO stands for "Identification – Attribution – Grading – Optimization." This general strategy is intended to provide a structured approach to any newly observed side effect – infections, as well as the recently emerging neurological complications of BCMA CAR T, or the development of tumors potentially associated with CAR-T treatment.

The first step involves identifying and describing side effects based on their frequency, severity, and persistence. The second step, "Attribution," focuses on whether the side effects can truly be causally linked to the treatment. The third step, establishing a grading system, involves evaluating the clinical impact of the side effect using a standardized system. Once established, all practitioners should use the grading and registries should capture it.

Last but not least comes "Optimization" – optimizing the management of the described side effects through new therapeutic approaches. "All of this," says Rejeski, "is the framework for gaining control over the challenge that is CAR T related toxicity." And a central task for the physicians and researchers who will be using CAR T cell therapy in the years to come.

Publication

Rejeski, K., Hill, J.A., Dahiya, S. *et al.* Noncanonical and mortality-defining toxicities of CAR T cell therapy. *Nat Med* (2025).
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The Medical Faculty of Ludwig Maximilians-University Munich and the LMU University Hospital make a significant contribution to the excellence strategy of the Ludwig Maximilians University in Munich.

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