Minimizing immunotherapy's potentially harmful side effects

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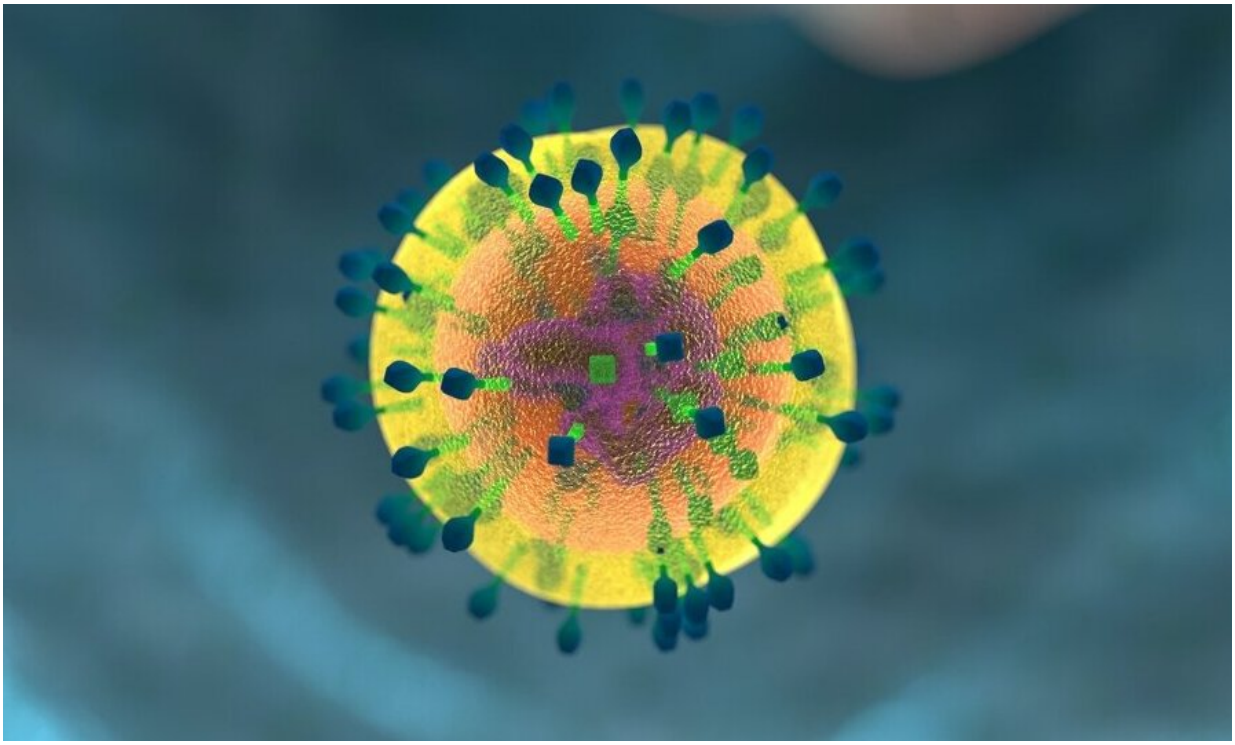

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Recent advances in treating multiple myeloma, the second most common blood cancer, and other blood malignancies are providing improved outcomes—and hope—to patients worldwide.

But treatment breakthroughs such as the immunotherapy drug

teclistamab can lead to potentially lethal side effects, including cytokine release syndrome (CRS) and immune cell-associated neurotoxicity syndrome (ICANS).

These potential side effects have necessitated giving immunotherapy drugs in the hospital setting, where patients remain for five to seven days and receive other drugs as needed to quell any immunotherapy complications.

Now, however, new research from Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine indicates that providing prophylactic treatment before immunotherapy can significantly reduce the rate of CRS in multiple myeloma patients.

The study, which appears in *Blood Cancer Discovery*, could eliminate the need to administer teclistamab and other immunotherapies in hospitals, thereby broadening access to countless more cancer patients.

"In an ideal world, you could pre-medicate patients against CRS and treat them in an outpatient setting," explained C. Ola Landgren, M.D., chief of the Division of Myeloma at Sylvester and co-corresponding study author. "As a result, there is huge interest in this possibility worldwide."

T-cell engagers

Teclistamab and similar immunotherapies are known as bispecific T-cell engagers—drugs that bind targets on both tumor cells and T cells, with the goal of getting T cells to attack and ultimately shrink tumors.

In a key clinical study published in the *New England Journal of Medicine*, teclistamab produced an overall response rate of 63% in multiple myeloma patients whose tumors had failed to respond to

multiple previous therapies or had become resistant to them. The drug received FDA approval for use with these patients in 2022, followed by two other bispecific T-cell engagers.

"These immunotherapy drugs work by revving the immune system's response against the tumor," Landgren explained. "But the process can lead to an overactive immune response, the hallmark of CRS."

Physicians often treat CRS with drugs that counteract the cytokine release that causes T cells to go into overdrive. Tocilizumab, for example, has been used for years to treat CRS from immunotherapies.

That's why patients receiving teclistamab typically need a multi-day hospital stay for monitoring during therapy, prompting some patients to forgo the therapy. "It's a big barrier for many patients," he said.

Landgren and colleagues were inspired to conduct their research after reviewing preliminary data from a 2022 study on multiple myeloma patients treated prophylactically with tocilizumab. That study showed the approach eased CRS in patients receiving a different bispecific T-cell engager than teclistamab.

In their study, which included 31 multiple myeloma patients, Landgren and collaborators reported that only 13% developed CRS after prophylactic treatment with tocilizumab. The results were in stark contrast to the 72% observed in an earlier study treating patients for CRS as symptoms arose. Additionally, patients in this newer study had less severe CRS and lower rates of its recurrence.

This preventive approach also appeared to ease ICANS, a second, less common side effect causing neurotoxicity.

"Prophylactic treatment with tocilizumab is now standard of care at

Sylvester for multiple myeloma patients receiving T-cell engagers," said Andrew Kowalski, PharmD, a hematology/oncology clinical pharmacist at Sylvester and the study's lead author. "We are ahead of the curve."

Similarly, patients receiving CAR-T cell immunotherapy also seem to benefit from prophylactic CRS treatment, according to the study's authors.

Future plans

Some questions about prophylactic treatment remain. Does it reduce the effectiveness of immunotherapy drugs? So far, the answer appears to be no, according to both Kowalski and Landgren. Can it benefit patients with other blood cancers? Yes.

"This preventive approach has the potential to be expanded into leukemias and lymphomas as well," Kowalski said.

The Sylvester researchers are preparing for future changes in treatment settings. They are quietly readying an outpatient service to deliver teclistamab and other emerging immunotherapies, anticipating that U.S. regulators may lift the hospital-stay requirement.

Landgren likened this evolution to a previous one with the cancer drug rituximab, which initially required monitoring in an intensive care unit but now can be given outside the hospital.

"The field of myeloma is probably one of the biggest examples of successful drug development in modern times," he said. "We are going with full steam into an era of immunotherapy."

More information: Emerging Strategies for the Prevention of Immune Toxicities Associated with T-cell-Engaging Cancer Therapies, *Blood*

Cancer Discovery (2024).