CAR T-cell therapy “can’t be controlled once it’s in [a patient],” notes senior author Michael Hudecek, MD, of Universitätsklinikum Würzburg in Germany. The main adverse event, cytokine release syndrome (CRS), can be life-threatening and is primarily managed with tocilizumab (Actemra; Genentech) or high-dose corticosteroids. Whether to add a suicide gene to the CAR construct has elicited interest, but no approved CAR therapies include such “kill switches.”

“I thought it would be cool if, instead, we had a pharmacologic on/off switch to steer the function of CAR T cells,” Hudecek says, “which would mean interfering at the level of signal transmission.” To that end, the Würzburg team, led by first author Katrin Mestermann, PhD, screened a panel of tyrosine kinase inhibitors and landed on dasatinib. Approved for certain blood cancers and developed to target the BCR–ABL fusion protein, dasatinib also blocks another kinase, LCK. This prevents phosphorylation of CD3ζ and ZAP70, as well as the induction of NFAT, a key transcription factor in activated CAR T cells.

Given that all current CAR constructs contain a CD3ζ domain, Hudecek figured dasatinib “could be of universal relevance” in modulating this live therapy. In vitro, his group showed that CD19-targeting CAR T cells were effectively inhibited—in terms of cytolytic activity, cytokine secretion, and proliferation—with the drug.

Importantly, dasatinib’s impact was reversible: CAR T cells regained function soon after drug removal, and their viability was unaffected. Similar results were obtained in a mouse model of lymphoma, and again, efficacy was not compromised.

As far as “remote control” options for CAR T-cell therapy go, dasatinib could be a good one to consider, says study coauthor Michel Sadelain, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY. “It acts rapidly, can be readily discontinued, and is already available.”

To investigate the drug’s potential in alleviating CRS, Hudecek collaborated with Sadelain using a mouse model developed by the latter’s team (Nat Med 2018;24:731–8). These mice, designed to develop acute, often fatal CRS upon receiving CAR T cells, fared much better if given dasatinib shortly after therapy infusion: At 48 hours, 70% were still alive compared with 25% in a control group.

Overall, “this is very timely work, and the science is sound,” says Marco Ruella, MD, of the University of Pennsylvania in Philadelphia, who was not involved in the research. The data do suggest that dasatinib is less effective at inhibiting actively proliferating CAR T cells, “as occurs in the clinic during CRS,” he points out. The timing of administration, then, “could be critical, and probably a preemptive approach would be more successful,” he adds. Sadelain agrees that “it may be important to give dasatinib early enough in the course of treatment to prevent CRS.”

Hudecek, too, points to research that has uncovered biomarkers to predict the risk of severe CRS following CAR T-cell therapy (Blood 2017;130:2295–306). “We could have a window of opportunity to intervene with these patients,” he says.

Directly comparing dasatinib with tocilizumab and corticosteroids in a future study would also be useful, Ruella thinks. “We’ll better understand the actual potency of this approach and its relative effects—versus standard CRS medications—on CAR T-cell function and survival,” he says. –Alissa Poh  ■

**XPO1 Inhibitor Approved for Multiple Myeloma**

Patients with multiple myeloma who have exhausted treatment options can now try selinexor (Xpovio; Karyopharm Therapeutics), but the first-in-class selective inhibitor of nuclear export that inhibits XPO1 can cause debilitating side effects.

The FDA granted conditional approval to selinexor in combination with dexamethasone for patients with triple-class refractory myeloma, meaning the disease no longer responds to three standard types of therapy. By preventing the shuttling of molecular cargo through XPO1, tumor suppressor proteins accumulate in the nucleus, blunting the expression of genes that can fuel cancer growth.

“Selinexor has a novel mechanism of action, and it appears to be active when all of our other major drug classes have failed,” says Paul Richardson, MD, of Dana-Farber Cancer Institute in Boston, MA, a lead investigator in the phase II, single-arm STORM trial of the drug. “It is a challenging drug to administer, but in one of the sickest populations of patients with relapsed and refractory disease that’s been studied to date, we saw a meaningful response rate—and in a subset of our patients, these responses proved durable.”

In the trial, 32 of 122 patients responded to selinexor plus low-dose dexamethasone (Blood 2018;132:598). Two participants achieved stringent complete responses, six exhibited very good partial responses, and the rest experienced partial responses. Responses lasted 4.4 months on average, with the longest duration of response exceeding 18 months.

Exploratory analyses also suggest a survival benefit. At the 2019 American Society of Clinical Oncology Annual Meeting in Chicago, IL, Richardson reported that STORM participants who received selinexor and dexamethasone right after their myeloma had become triple-class refractory lived a median of 10.4 months (J Clin Oncol 2018;37, 2019 [suppl; abstr 8014]). In comparison, patient records in the Flatiron Health Analytic Database indicated a median survival of 5.2 months for patients who received other types of therapy. Richardson describes the survival data as “supportive” of the favorable responses observed in STORM and other trials.

Selinexor’s safety profile proved less auspicious. In the STORM study, 89% of patients experienced a serious (grade 3 or worse) drug-related adverse event, with most decreasing the drug or discontinuing treatment. At least two participants died because of selinexor-associated toxicities—one from sepsis, the other from pneumonia. (Eight other adverse event-related deaths could not be directly attributed to the drug.) Additionally, patients...
against it. "Without randomized data," he says, "I can’t fathom that cost."

–Elie Dolgin ■

New ADC Shrinks HER2-Positive Tumors

A novel antibody–drug conjugate (ADC) triggers responses in patients with HER2-expressing breast cancer and other solid tumors, a phase I clinical trial indicates (Lancet Oncol 2019;20:1124–35). The drug could become a new treatment for patients with breast cancer who are resistant to the ADC trastuzumab emtansine (Kadcyla, T-DM1; Genentech) or who have low HER2 expression.

T-DM1, a second-line treatment for patients with HER2-positive breast cancer, kills cells by inhibiting microtubule polymerization. However, patients usually develop resistance, prompting researchers to develop new ADCs. The ADC tested in the current trial, trastuzumab duocarmazine, also targets HER2-expressing cells, but its payload triggers DNA damage.

The dose-escalation portion of the trial included 39 patients with advanced or metastatic solid tumors, each of whom received 0.3 to 2.4 mg/kg of trastuzumab duocarmazine. One third of the patients reported grade 3 or 4 side effects, including fatigue and neutropenia. Many also experienced eye problems, with 31% developing conjunctivitis, keratitis, and dry eye. These adverse effects have been seen with other ADCs—although they haven’t been described with T-DM1—but the mechanism remains unclear, says co-author Philippe Aftimos, MD, of the Jules Bordet Institute and the Free University of Brussels in Belgium.

The ADC produced partial responses in 33% of the patients with HER2-positive metastatic breast cancer; 28% with HER2-low, HR-positive metastatic breast cancer; and 40% with HER2-low, HR-negative metastatic breast cancer. The median progression-free survival for these three groups was 7.6 months, 4.1 months, and 4.9 months, respectively. The researchers also saw signs of drug activity in the patients with other cancer types: Partial responses occurred in 25% of patients with urothelial cancer and 39% of those with endometrial cancer.

The results suggest that patients with HER2-positive breast cancer resistant to T-DM1 “can still respond to other ADCs with different payloads,” says co-author Udai Banerji, MD, PhD, of the Institute of Cancer Research and The Royal Marsden NHS Foundation Trust in London, UK. Because trastuzumab duocarmazine works through a different mechanism, it may kill cells that are resistant to T-DM1, he says.

Patients with breast cancer and low HER2 expression, for whom there are no approved anti-HER2 therapies, could also benefit from trastuzumab duocarmazine, says Aftimos. “We have proof that targeting HER2 in HER2-low breast cancer is an effective strategy.” Although trastuzumab alone does not benefit these patients, the ADC may work through a bystander effect, allowing it to kill adjacent tumor cells even if they don’t overexpress HER2, he says.

The trial was too small to confirm that “this drug works at a substantial level in patients who have progressed on T-DM1,” cautions Ian Krop, MD, PhD,