patients for CAR T-cell therapy—might have been to blame. Fludarabine was removed from the regimen, and the FDA allowed ROCKET to proceed. However, after two more deaths due to cerebral edema occurred, the company elected to shelve JCAR015.

One of the key findings from Juno’s retrospective analysis, Gilbert noted, was that all five patients who died experienced rapid, early expansion of their modified CAR-bearing T cells within a week of being infused, rather than the typical time frame of 12 to 14 days. High levels of the CD8+ subtype and, consequently, a sharp spike in cytokines such as IL2 and TNFα produced by these cytotoxic cells, were significantly correlated with fatal brain swelling, Gilbert added.

Autopsy results from two patients showed a complete breakdown of the blood–brain barrier, possibly due to this inflammatory cytokine surge, which—in line with findings from an unrelated study—may have driven their cerebral edema (Cancer Discov 2017;7:1404–19). “It wasn’t what I expected,” said ROCKET’s lead investigator Daniel DeAngelo, MD, PhD, of Dana-Farber Cancer Institute in Boston, MA. He had thought the culprit would be CAR T cells or other immune cells infiltrating the brain.

Gilbert also reported that the patients who died were younger than 30 and had received fewer prior therapies. As well, they had higher baseline levels of IL15, another T-cell growth factor. Going on to look at ROCKET’s population as a whole, he noted that “those with Philadelphia chromosome–positive disease seemed to have a much better outcome with regard to the overall risk of neurotoxicity—an interesting signature we’re trying to confirm through a larger study.”

However, Gilbert cautioned that findings from Juno’s internal investigation shouldn’t be considered definitive, because “this wasn’t a planned analysis, but exploratory in nature.”

The company is moving ahead with additional CAR T-cell therapies, including evaluating JCAR017 in patients with relapsed or refractory non–Hodgkin lymphoma. Lessons learned from ROCKET have been duly applied: For instance, patients no longer receive infusions of a product with wide variability in its T-cell composition. Instead, JCAR017 consists of a fixed ratio of CD8+ cells as well as the CD4+ “helper” subtype. Its CAR construct also has 4-1BB, rather than CD28, as the costimulatory domain, which may better control the pace of cell proliferation. Eventually, Juno hopes to test this therapy in ALL, Gilbert said.

After JCAR015’s failure, “the question was, ‘should we even try CAR T-cell therapy in adult ALL?’” DeAngelo remarked. “The reality is that we saw a high, confirmed complete remission rate [47%]. We need to better control the product and also focus on patient characteristics that might predispose to neurotoxicity, but I still think this is the way to go.” –Alissa Poh ■

**FDA Approves Second CAR T-cell Therapy**

The FDA approved the chimeric antigen receptor (CAR) T-cell therapy axicabtagene ciloleucel (Yescarta; Kite Pharma) in late October, the second such treatment for blood cancers in the United States.

Axicabtagene ciloleucel is indicated for the treatment of adults with certain non-Hodgkin lymphomas, including diffuse large B-cell lymphoma, the most common form. Patients must have relapsed after, or not responded to, at least two other treatments before receiving axicabtagene ciloleucel. Treatment involves collecting and genetically modifying a patient’s T cells to express CARs so that they bind to and destroy CD19-expressing cancer cells and normal B cells.

The safety and efficacy of axicabtagene ciloleucel were established in a multicenter clinical trial of more than 100 adults with refractory or relapsed large B-cell lymphomas. The complete remission rate was 51%.

The first FDA-approved CAR T-cell therapy, tisagenlecleucel (Kymriah; Novartis), was approved in August. The two therapies work in much the same way, but they have different indications, with tisagenlecleucel approved to treat only acute lymphoblastic leukemia in patients age 25 or younger. “These approvals represent a very important development in modern cancer treatment,” says Steven Rosenberg, MD, PhD, chief of the Surgery Branch at the NCI. “These treatments are very effective in patients with lymphomas and leukemias,” he notes, adding that the first case study of CAR T-cell therapy was published in 2010, and that patient remains cancer-free. Rosenberg led the team that originally developed the therapy.

Axicabtagene ciloleucel carries boxed warnings for two potential fatal side effects: neurologic toxicity and cytokine release syndrome (CRS), a flu-like systemic response to the proliferation of CAR T cells. In the phase II ZUMA-1 trial, CRS occurred in 94% of patients; 13% of patients experienced symptoms that required aggressive treatment or were considered life-threatening.

For this reason, axicabtagene ciloleucel’s use requires a risk evaluation and mitigation strategy. Sites administering the treatment must obtain special certification, including training on recognizing and managing side effects. Currently, 16 facilities are certified to dispense axicabtagene ciloleucel. Kite hopes to increase that number to 70 within the next 12 months.

The list price of axicabtagene ciloleucel is $373,000. However, the personalized nature of the treatment, the extensive monitoring program, and the relatively high response rate may justify the expense. “The best way to save clinical care dollars is to cure people rather than moving them from one
Neoantigen Quality Predicts Immune Response, Survival

It’s the quality, not quantity, of tumor neoantigens that may best predict response to immunotherapy and the likelihood of long-term survival among patients with cancer.

A team led by Marta Łuksza, PhD, of the Institute for Advanced Study in Princeton, NJ, and Benjamin Greenbaum, PhD, of the Icahn School of Medicine at Mount Sinai in New York, NY, combined concepts from immunology, evolutionary biology, physics, and computer science to study how the immune system recognizes tumors, and how tumors mutate and evolve in response, especially in the face of checkpoint inhibition.

The researchers developed a mathematical model and tested it on three data sets—two cohorts of patients with melanoma given anti–CTLA4 therapy, and a group with non–small cell lung cancer given anti–PD-1 therapy (Nature 2017;551:512–16). All had undergone surgery and some had received adjuvant chemotherapy, but immunotherapy was not part of the treatment regimen. Initially, the team found that tumors with the highest neoantigen number and the most abundant cytotoxic T-cell infiltrates—but neither alone—stratified patients with the longest survival. Digging into possible reasons, they showed that long-term survivors displayed lasting circulating T-cell reactivity to high-quality neoantigens, as defined by the fitness model. Because this approach worked for three different tumor types, two flavors of checkpoint inhibitor, and two different clinical settings—with or without immunotherapy—“our data may be identifying some common principles on how the immune system recognizes mutations,” says Balachandran.

Elizabeth Jaffee, MD, of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University in Baltimore, MD, isn’t yet convinced. “It’s an interesting model,” she says, but points out that, in the context of pancreatic cancer, it’s so far been tested only in a unique subset of patients that may not represent the population as a whole. How relevant is this going to be, she asks, for the 93% of patients who don’t survive beyond 5 years with surgery alone, but may do so with newer therapeutic interventions?

Balachandran and his colleagues next plan to see if the model predicts response rates to immunotherapy among participants in the Pancreatic Cancer Action Network’s Precision Promise trial. Additionally, his team is engaging with Genentech and Mainz, Germany–based BioNTech to determine how insights gleaned from this work can be applied to trials of personalized mRNA-based neoantigen vaccines.

“Pancreatic cancer is a challenge, given the relatively low number of mutations harbored by these tumors,” says Ugur Sahin, MD, BioNTech’s cofounder and CEO. “It’s also considered a ‘cold’ tumor, with very few infiltrating T cells. The new findings upend this conventional wisdom, Sahin says, and “strongly suggest” that even pancreatic cancer might be responsive to a neoantigen-based therapeutic strategy. –Elie Dolgin

Wild Microbiome Stems Tumorigenesis in Lab Mice

Despite the many therapies that owe their foundation to findings in mouse models, there’s a growing appreciation among scientists that typical lab mice—and, more specifically, the effects of their sterile environs—do not always accurately reflect real-world diseases. Now, a recent study has found that simply replacing their gut microbiome with the microbes of wild mice alters the animals’ immune response, perhaps for the better (Cell 2017;171:1015–28).

The lab mice who received a microbial boost from their wild counterparts were more resistant to inflammation-driven diseases, the authors report, including colorectal cancer and flu.

“Our starting hypothesis was that in nature, the microbiome has co-evolved with its host for millions of years and probably has beneficial health effects that we do not see in laboratory mice,” says study author Barbara Rehemann, MD, of the National Institute of Diabetes and Digestive and Kidney Diseases.

To test that hypothesis, the authors trapped more than 800 wild mice in barns in eight different locations around Maryland and Washington, DC. They characterized the gut microbiota of 98 of these mice using ribosomal RNA profiling and found that the barn animals’ microbiomes, though similar to each other, were very different from those of the laboratory mouse strain C57BL/6. The lab animals’ microbiomes were less complex and were deficient in certain bacterial species present in the wild animals, chiefly Bacteroidetes and Proteobacteria.

The researchers isolated wild gut microbiomes and those from laboratory mice and transplanted them into separate groups of laboratory mouse pups reared without microbes. Using a chemical mutagen and a colitis-inducing compound to trigger...
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