ILLUSTRATION BY ELIN SVENSSON

DRUG SAFETY

The struggle to do no harm

What lessons are being learnt from clinical trials that went wrong?

BY CHARLES SCHMIDT

Most people who enter a clinical trial for a cancer immunotherapy have advanced disease. They hope that the treatment, which aims to activate their T cells against cancer, will boost their life expectancy from months to years. In rare cases, however, the pendulum swings the other way and the treatment results in a fatal reaction.

Deaths in recent trials for three cancer immunotherapy drugs have put participants, researchers and drug companies on edge, largely because the causes of the deaths are not well understood.

"These agents can produce autoinflammatory responses that we know shockingly little about," says Jeffrey Weber, deputy director of the Laura and Isaac Perlmutter Cancer Center at the New York University Langone Medical Center.

Harriet Kluger, a medical oncologist at Yale Cancer Center in New Haven, Connecticut, says that the deaths underscore the challenges of trying to predict which of the participants might be affected by the worst complications of treatment. "On balance, immunotherapy's risks don't outweigh the potential benefits for cancer patients," she says. "But we also need to be very careful when giving these therapies, because some individuals are going to suffer serious toxicities that we can't reverse."

STORM PREDICTION

In August 2017, a 78-year-old man died after being treated with an experimental immunotherapy called UCART123. Developed by French biopharmaceutical company Cellectis, UCART123 is a chimaeric antigen receptor (CAR) T-cell-based drug. It was being tested in a pair of phase I trials — one for a rare and aggressive type of leukaemia called blastic plasmacytoid dendritic cell neoplasm, which was the man's diagnosis, and the other for acute myeloid leukaemia. The US Food and Drug Administration (FDA) immediately suspended both trials. The death followed those in 2016 of five adults with acute lymphoblastic leukaemia who were receiving a CAR T-cell therapy called JCAR015, developed by Juno Therapeutics of Seattle, Washington. Juno (which is defending itself against a class-action lawsuit about the JCAR015 trial) did not respond to *Nature*'s requests for interview. Cellectis acknowledges that there is a knowledge gap. "Scientists still have much to learn about how injected CAR-T cells will react and expand in the patient," says chief executive André Choulika. "This will be a global effort."

Most CAR T-cell therapies such as JCAR015 are made by collecting, and then genetically engineering, a person's T cells so that the cells express an artificial receptor protein: the CAR. After they are put back in the body, the modified T cells kill off any cells that express the antigen CD19, including the malignant B cells that occur in blood cancers. (UCART123 takes an alternative approach, using the same basic mechanism but without the T cells being targeted to specific patients.) The first commercialized CAR T-cell therapy, tisagenlecleucel, developed by Novartis in Basel, Switzerland, received approval from the FDA in August for use in young people with acute lymphoblastic leukaemia.

But because normal B cells also express CD19, CAR T-cell treatments can unleash a torrent of off-target effects. Stephan Grupp, director of cancer immunotherapy at the Children's Hospital of Philadelphia in Pennsylvania, says that the engineered T cells bypass the body's usual checks on immunity, and proliferate so quickly that those who are treated with them can end up in intensive care. Many recipients develop cytokine release syndrome (CRS), an extreme inflammatory reaction involving a 'storm' of immune-system molecules that, at its mildest, triggers a condition resembling a nasty bout of influenza. However, when it rages uncontrollably, CRS can lead to sepsis and multiple organ failure. The man in the Cellectis trial died of CRS, and the five Juno-trial participants died from swelling of the brain related to CAR T-cell therapy.

The amount of inflammation produced in response to CAR T-cell treatments tends to correspond with the amount of cancer in the body, so people with more extensive disease will experience greater side effects. But apart from that general rule of thumb, doctors don't know why some people experience worse reactions than do others, and drug recipients can react badly on a moment's notice, says Elizabeth Budde, an oncologist at City of Hope, a cancer treatment centre in Duarte, California.

The Juno and Cellectis trials gave CAR T cells to the participants after pretreating the individuals with fludarabine, a chemotherapy drug that depletes the body of T cells, so that the population of engineered cells has a better chance to expand. Fludarabine has been used

widely with CAR T cells made by other companies without known problems.

After the first three Juno trial participants died, representatives from the company suggested the cause was the interactions of fludarabine with JCAR015, rather than the immunotherapy drug itself. The FDA paused the trial but then let it resume, several days later, on the condition that the pretreatment with fludarabine was discontinued. However, the situation soon became more complicated. Two more participants died, despite being on the fludarabine-free protocol. At that point, Juno pulled JCAR015 from development altogether.

Grupp is unconvinced that the fludarabine pretreatment contributed to the deaths. "We've treated 150 kids with fludarabine and never had any problems," he says.

Budde points out that deaths associated with CAR T-cell therapy aren't unique to either the Juno or Cellectis trials. According to Budde, clinicians can monitor people for CRS by checking for fever, changes in blood pressure and elevations in the blood of a marker for inflammation called C-reactive protein. And researchers at the Fred Hutchinson Cancer Center in Seattle, Washington, have shown that a fever exceeding 38.9 °C that arises up to one and a half days after treatment plus high levels of the cytokine MCP-1 can also predict CRS (K. A. Hay *et al. Blood* **130,** 2295–2306; 2017).

A drug approved by the FDA in August 2017 can potentially reverse CRS to pull those with the condition back from the brink of death. Wary of interfering with anticancer immunity pathways, doctors used to give the drug — called tocilizumab — only when people with CRS were dangerously ill. But Budde says that there is evidence to show it is possible to give tocilizumab before CRS even occurs, without comprising the efficacy of CAR T-cell therapy. Doctors can monitor people for neurotoxicity by looking for signs of confusion, cognitive decline, and high levels of MCP-1 and another cytokine, interleukin-6, and then treat the neurotoxic side effects with steroids that cross the blood–brain barrier.

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Companies are also tinkering with designs for CAR T cells that might be less toxic. A particular set of design choices focuses on the co-stimulatory domain, a part inside the engineered T cell that helps to boost the inflammatory response. Budde points out that the CAR T cells in the Juno trial contained one such molecular booster called CD28, which triggers a rapid and potent inflammatory response that dies out fairly quickly. Another co-stimulatory domain design option called 4-1BB isn't as potent but acts for a longer duration. "It's hard to say if one is better than the other," says Budde.

In November 2017, Juno scientists presented an early analysis of the JCAR015 deaths that pointed to surpisingly early and rapid proliferation of the CAR T cells. Risk of fatal brain swelling also was associated with pre-existing levels of the cytokine IL-15 (a growth factor for T cells), variable dosing and several other factors.

CHECKPOINT INHIBITORS UNCHECKED

Deaths have also complicated the prospects for drugs that target programmed cell death protein 1 (PD-1), a molecular brake on overactive immunity that malignant cells exploit for protection. This cell-surface protein acts as a checkpoint, neutralizing T cells and rendering them inactive against cancer (see page S72). Drugs known as checkpoint inhibitors that target PD-1 (or its ligand on the tumour cell, known as PD-L1) have fewer off-target effects than CAR T-cell treatments, and are therefore considered to be safer.

But in July 2017, after interim results showed that more participants had died in the treatment groups than in the control groups, the FDA halted two phase III trials that were testing the PD-1 inhibitor pembrolizumab in people with multiple myeloma. Pembrolizumab — a blockbuster immunotherapy drug developed by Merck of Kenilworth, New Jersey — is already approved for use with a variety of solid tumours.

The complete halt to the trials, also known as a full clinical hold, was not just a blow for Merck. Two other pharmaceutical companies were developing PD-1 inhibitors as therapies for blood cancers: New York-based Bristol-Myers Squibb, which is testing a PD-1 inhibitor called nivolumab in people with multiple myeloma; and AstraZeneca, in Cambridge, UK, which is conducting clinical trials of the drug durvalumab for lymphoma and chronic lymphocytic leukaemia.

Citing safety concerns that arose from the Merck studies, the FDA put a partial clinical hold on the Bristol-Myers Squibb trial, preventing the enrolment of new participants but allowing existing ones to remain on the experimental therapy.

The Merck trials combined pembrolizumab with one of two other immunity-modulating drugs used to treat multiple myeloma: lenalidomide and pomalidomide. Both are typically given with a steroid called dexamethasone. A phase I study by Merck had shown that people who stopped responding to lenalidomide become sensitive to it again after being treated with pembrolizumab. (Notably, pomalidomide is given to people with multiple myeloma who do not respond to lenalidomide.) The combination seemed to be safe in the earlier study. But in the phase III clinical trials, the combined treatments resulted in worrying death rates.

In one of those trials, Keynote 185, 19 people died in the group who received pembrolizumab and lenalidomide with dexamethasone, compared with 9 of the group who were given only lenalidomide and dexamethasone. In the other Merck trial, called Keynote 183, 29 people treated with pembrolizumab and pomalidomide with dexamethosone died, compared with 21 people from the pomalidomide with dexamethasone control group. Deaths during the trials were attributed to a range of causes, including heart attack, heart abnormalities, sepsis, multiple organ failure and respiratory tract infections.

Weber describes those deaths as a mystery that probably had more to do with the effects of combining pembrolizumab with lenalidomide or pomalidomide than a specific consequence of PD-1 inhibition, which is otherwise considered to be safe. "If PD-1 inhibition alone had caused the deaths, wouldn't we also see them in other trials with PD-1 inhibitors?" he asks.

Roy Baynes, senior vice-president of global clinical development at Merck, adds that participant selection could have played a part in the excess mortality. As evidence, he points out that the deaths in the Keynote trials had no shared cause. "They weren't due to malignant progression, and no single class of adverse events was disproportionately represented," he says. "It could merely be that these patients were very ill and older with other significant health problems." However, he says, "the FDA's abundant caution in putting the trials on hold was correct".

WATCHING THE DETECTIVES

Identifying the causes of death in the Cellectis, Juno and Merck trials requires medical detective work, says Weber. This will entail the cooperation of clinical investigators, drug companies and the FDA. The FDA is also conducting its own independent investigations. In November, the agency gave the go-ahead to resume trials of UCART123, with further precautions.

In the case of the Merck trials, an essential question is whether the PD-1 inhibitor interacted with pomalidomide or lenalidomide in unexpectedly lethal ways. Weber thinks that studies in cells and mice will help to answer that question. "You also have to consider the timing of treatment," Weber says. "Did deaths occur at the time of therapy or later on? Were the deaths associated with side effects that we can reasonably ascribe to other drugs?"

"This is the nature of the clinical-trials business: you do a study, you get a toxic signal, people look into it, and a decision is made to put the trials on hold," he adds. "There's always the potential for toxicity and these patients were very sick to begin with."

These studies of three drugs are just a few among thousands of ongoing clinical trials in immunotherapy, and the high rewards for some participants will be accompanied by the potential risk of death for others. Clinicians will try as best they can to minimize that risk. But until the threats from immunotherapy are better understood, some treatment outcomes will remain unpredictable. ■

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CORRECTION

The Outlook article 'The struggle to do no harm' (*Nature* **552,** S74–S75; 2017) mistakenly claimed that the biopharmaceutical firm Cellectis had not responded to requests for interview. A comment from the company is now included in the online version of the story, at go.nature.com/2owayrn.