CANCER IMMUNOTHERAPY

Worries, confusion after cancer trial deaths

Experimental immune treatment linked to fatal brain swelling

By Jennifer Couzin-Frankel

An experimental cancer therapy is facing its biggest setback yet, after an unexpected complication killed seven people over about a year, five of them in a single clinical trial. The company, Seattle, Washington-based Juno Therapeutics, has its most troubled trial on hold and is racing to figure out why patients suffered fatal brain swelling. Researchers elsewhere are grappling with possible ramifications for the breakthrough treatment, which goes up for drug approval next year.

"Why would we see this now? We don't know, period," says Stephan Grupp, a pediatric oncologist at the Children's Hospital of Philadelphia in Pennsylvania. In several trials, he has treated more than 100 children with the experimental approach, in which a patient's own immune cells are genetically engineered to fight cancer. None experienced the fluid buildup, known as cerebral edema, that killed adults in Juno's trials. Grupp and others speculate that the explanation may lie in the specific product tested and the patient population, rather than in the overall strategy itself. Still, they are mostly in the dark. Cerebral edema "wasn't on anybody's radar," Grupp admits. Company officials declined to comment, saying only that they are investigating.

Several hundred people with advanced blood cancers, from toddlers to seniors, have received the treatment, called chimeric antigen receptor (CAR)-T cell therapy, with remarkable results (Science, 28 June 2013, p. 1514). Many have now been cancer free for years, and the therapy is part of a new arsenal of immune-based cancer therapies (Science, 20 December 2013, p. 1432). Doctors are beginning to test CAR-T therapy in solid tumors like lung cancer. Results there are mixed (Science, 2 September, p. 983).

Like other cancer immunotherapies, CAR-T therapy can overstimulate the immune system, triggering an out-of-control proliferation of immune cells that can shut down vital organs. The first child treated with CAR-T therapy, a 6-year-old girl with leukemia, nearly died from this. "The community recognized this as a huge threat to our patients and to the therapy" and found drugs to manage it, says Crystal Mackall, who heads the cancer immunology and immunotherapy program at Stanford University in Palo Alto, California. The therapy was also known to carry neurological risks, including confusion, delirium, seizures, and even a temporary inability to speak. But they have not been fatal.

Juno reported the first death about a year ago, but it didn't trigger alarm bells. Then in July, the company revealed a cluster of three more deaths in a different trial, for acute leukemia. Juno suggested these were due to a chemotherapy drug called fludarabine that the patients also received. Juno eliminated fludarabine from its protocol, and the U.S. Food and Drug Administration (FDA) allowed the trial to resume.

But late last month, edema killed two more patients in the same trial, which is now back on hold. Neither the company nor FDA has released much information since, including the total number of patients treated. Last weekend at the annual American Society of Hematology (ASH) meeting, however, Juno reported that a seventh patient, with chronic leukemia, had also died from cerebral edema.

Mackall and others wonder whether the edema is essentially an extreme version of the brain issues doctors were already recording or is something else. Either way, the cause could lie in one or several specific features of the Juno trial. For one, most of the deaths are in adults with acute leukemia; people with this disease tend to have more side effects from CAR-T therapy, in part because the T cells can expand more quickly for reasons that are not well understood. This increases effectiveness but also risks. Other variables include the age of trial participants—children often have fewer side effects—and the chemotherapy given before the T cells.

Finally, there's the design of the CAR-T cells themselves. All incorporate a "costimulatory molecule" that encourages proliferation. The five deaths occurred in Juno's trial that uses a molecule called CD28. The company's other trial, with two edema deaths, relies on a different molecule, called 4-1BB. Novartis, which is also running trials in acute leukemia and has not reported cerebral edema, relies on 4-1BB, too.

A third company, Kite Pharma, based in Santa Monica, California, is using CD28 but is treating adults with advanced lymphoma, not leukemia; it hasn't seen any cases of cerebral edema, executives say. Kite and Novartis plan to apply for FDA approval next year.

Better animal models could help solve the mystery. The most popular CAR-T therapy model, in mice, failed to predict any neurotoxicity. Earlier this week, a team at the Seattle Children's Research Institute in Washington reported that they had tested a CAR-T therapy in rhesus monkeys, and that the animals developed abnormal behaviors and tremors, suggesting neurologic effects.

"It's clearly sobering," Mackall says of the Juno deaths. "I've lived, eaten, and breathed" this therapy, and "you think you understand it." Still, she points out, all cancer drugs come generally accept given the severity of the disease. "Let's get rid of the hype here: This is a new therapy that is very promising," Mackall says, "but we still have a lot to learn about it."
Editor's Summary

This copy is for your personal, non-commercial use only.

**Article Tools**
Visit the online version of this article to access the personalization and article tools:
http://science.sciencemag.org/content/354/6317/1211

**Permissions**
Obtain information about reproducing this article:
http://www.sciencemag.org/about/permissions.dtl