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# Infant with deadly leukemia saved by drug for adult liver cancer

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UCSF Benioff Children's Hospitals have successfully treated a months-old infant with a rare childhood leukemia using a targeted therapy approved for adults with inoperable liver cancer and advanced kidney cancer.

The decision to use the drug, sorafenib, was made after pathologists identified a unique mutation in the form of two genes being fused together instead of on separate chromosomes—according to a case study publishing in the journal *Leukemia* on Sept. 11, 2019.

The patient, now a thriving toddler, personifies a growing shift in cancer treatment: the genes fueling the cancer, rather than the type of cancer itself, may determine optimal therapy, say researchers, led by senior author Elliot Stieglitz, MD, a physician scientist in the UCSF Division of Pediatric Hematology/Oncology and the Helen Diller Family Comprehensive Cancer Center.

The authors report that the infant presented with the hallmarks of leukemia, including enlargement of the liver and spleen, and elevated white blood cell counts.

The child was believed to have JMML, or juvenile myelomonocytic leukemia, an aggressive type of blood cancer most commonly affecting infants and toddlers, and occurring in about 1.2 children per million, per year. JMML is treated with a stem cell transplant, in which intense chemotherapy is given to wipe out JMML cells, followed by a transplant

of donated stem cells from a closely matched donor into the recipient's bone marrow, where they produce healthy blood cells. However, up to 50 percent of JMML patients relapse after transplantation.

## Live-Saving Treatment Stalled When Infant's Condition Declined

Chemotherapy was initiated in an attempt to reduce the disease burden before stem cell transplant, said Stieglitz. "Unfortunately, the patient did not respond to chemotherapy and his symptoms worsened. The stem cell transplant was no longer an option."

Facing shrinking options, Stieglitz's team conducted molecular profiling of the child's cancer cells, in the hope that mutations could be identified and matched with targeted therapies. They used both UCSF 500, a cancer gene panel that sequences DNA from a patient's cancer cells and compares them to normal tissue, and a second tool that analyzes RNA, which offers a more sensitive measurement of gene expression and may identify novel features, including fusion genes. None of the mutations associated with JMML were found. However, the pathologists were surprised to discover a mutation known as an FLT3 fusion—something that had never before been reported in a pediatric malignancy, the authors said.

"We know that fusions are more likely to respond to targeted therapies than other types of mutations," said Mignon Loh, MD, a co-author and Chair in Pediatric Molecular Oncology, who was involved in the patient's care. "Sorafenib, which was developed at UCSF, is a type of targeted therapy known as a kinase inhibitor that works by blocking the action of an abnormal protein that signals cancer cells to multiply."

After two weeks on sorafenib, the patient's white blood cell counts

plummeted to within the normal range. After 10 weeks' treatment, the infant was well enough to undergo a stem cell transplant. Sorafenib was stopped after nearly two years. The patient remains in remission months later.

"The patient's history reveals that the one-size-fits-all treatment approach does not work well for all children with JMML," said Stieglitz. "The course of JMML is highly variable. In rare cases, children spontaneously go into remission with minimal treatment, while half of all patients suffer from a highly aggressive form of the disease that fails to respond to stem cell transplant."

Most JMML patients present with genes that hyperactivate the Ras pathway, said Stieglitz, referring to a chain of proteins within the cell that communicates a signal from a receptor to the DNA in the nucleus.

"Recently there have been reports of JMML patients who have lacked these Ras mutations, but have fusions like our patient," he said. "We recommend that all patients without Ras mutations undergo RNA sequencing to identify any fusions that might be treated with targeted therapies."

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