Breaking Down HIV Exclusions in Cancer Clinical Trials

As an eligibility barrier cracks, a lung cancer patient gets a new lease on life.

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For reasons that date back to the earliest days of the AIDS epidemic, HIV-positive people with cancer have often been excluded from cancer clinical trials. Now, that may be changing.

On Sunday, at the annual meeting of the American Society of Clinical Oncology, the nation's top cancer doctors learned the results of a new study led by physicians at Fred Hutchinson Cancer Research Center in Seattle. It showed that patients with HIV and one of a variety of potentially deadly cancers could be safely treated with the immunotherapy drug pembrolizumab, also known by its brand name, Keytruda.

During an ASCO presentation concurrent with the release of the study in JAMA Oncology, Hutch researcher and lead author Tom Uldrick, MD, said that in nearly all cases it was safe to use the drug in patients with cancer and HIV. The "adverse events profile," a measure of the safety of the drug in the study, was not substantially different from prior studies that excluded such patients. The results, study authors said, are likely applicable to five similar drugs that block receptors known as PD-1 or PD-L1 on the surface of T cells.

"Our conclusion is that anti-PD-1 therapy is appropriate for cancer patients with well-controlled HIV, and that patients with HIV and cancer can be treated with the drug and should be included in future immunotherapy studies," Uldrick said in an interview prior to the conference.

One participant's story

Although the primary purpose of the study was to evaluate safety, it also provided a snapshot of the anti-cancer activity of the drug on these patients. For one of those patients, the trial turned out to be a lifesaver.

Joe Hall, 56, received his first infusion of Keytruda in April 2015 at the National Institutes of Health Clinical Center. He had an aggressive lung cancer that had swiftly come back despite treatment. He has also been HIV-positive since 1989. For the Fort Myers, Florida, resident, the decision to participate was straightforward: "There wasn't even a hesitation to sign up," Hall said. "The options for me, they were bleak."

Although he can't say for sure, he thinks he felt his immune system start to wake up that very same day — like he was fighting off a cold.

About two months later, he and his husband, Jeff, sat down with one of the study doctors at the NIH. The doctor put two scans up on her screen: the before and the after.

As they surveyed the remnants of his tumors — "They looked like they were exploding into cotton candy," Hall said — he and his husband started to cry with surprise and relief.

"I didn't have any idea what to expect," Hall said. "The best I'd expected was to keep it in check."

Today, Hall's doctors consider him a "complete responder" — that is, they do not see any evidence of tumors. While continuing his regular Keytruda infusions, he is back to his regular life. He works long hours at the business where he is a partner. And, he points out with pride, he can still hit the high tenor notes in his church choir, even with only one lung.

Hall's case is not typical: He is the only patient on the trial who had a complete response. Yet it is "reassuring" to see such an outcome in an HIV-positive person with lung cancer, as is sometimes seen in other patients with this cancer, said Uldrick, who cared for Hall on the trial.

Hall says he hopes his story offers hope to people facing advanced cancers — and that it helps educate doctors that HIV-positive cancer patients like him might be candidates for drugs like Keytruda.

"The word needs to get out," he said.

Addressing cancer in people with HIV

The study findings strengthen the case for opening the door to cancer clinical trials for people with HIV, a door that has begun to crack open. The National Cancer Institute has encouraged inclusion of HIV-infected patients on clinical trials since 2008, and the Food and Drug Administration in March circulated for comment a draft of non-binding guidelinescalling for appropriate inclusion of people with HIV, hepatitis B or hepatitis C in cancer clinical trials. This is the first of two NCI-sponsored trials specifically testing whether a class of cancer immunotherapy drugs called checkpoint inhibitors is safe in patients with HIV.

"Exclusion of people with HIV in clinical trials is a longstanding problem that grew out of the poor outcomes of AIDS patients with cancer, before there were effective antiviral therapies for HIV," Uldrick said. In prior research, Uldrick surveyed 46 recent clinical trials that led to the approval of cancer drugs, and he found 30 contained explicit exclusions for patients with HIV, and nine others where an exclusion was implied.

The 30-patient trial studied Keytruda, an anti-PD-1 therapy. Keytruda is manufactured by Merck, which provided the study drug to the trial sponsor, the NCI. HIV-positive patients with different cancers that might respond to the drug were included in the trial. In addition to lung cancer, other cancers treated were Kaposi sarcoma, or KS; non-Hodgkin lymphoma; liver cancer; anal cancer

and advanced squamous cell skin cancer.

The study was conducted at seven different cancer centers across the United States, including the NCI's HIV and AIDS Malignancy Branch in Bethesda, Maryland.

Safety issues addressed in the trial include whether the known side effects of the drug, such as gastrointestinal distress and skin rash, were more problematic in HIV patients. The researchers were also watching for unanticipated disturbances in their immune system, such as an unhealthy or uncontrolled surge in T cells. "Many cancer researchers just assumed that checkpoint inhibitor therapy, which relies on patients' T cells to fight cancer, would not be effective in HIV-infected individuals," noted Robert Yarchoan, MD, chief of NCI's HIV and AIDS Malignancy Branch. The trial allayed those worries.

Another concern was whether the drug might unmask an underlying opportunistic infection, and here the study encountered an unexpected problem. One participant in the trial, enrolled for the treatment of KS, died of a noncancerous condition involving KSHV, the virus that causes KS, and overproduction of certain white blood cells. Although a link between the patient's death and use of the drug is unclear, the study authors recommend that patients with HIV who have high levels of KSHV and symptoms of a condition known as multicentric Castleman disease — which is also linked to the virus and affects white blood cells — be tested before considering the cancer drug.

Opening the door to trials
HIV patient advocates and their oncologists are accustomed to the roller coaster of new drug trials and managing unexpected side effects, which can occur in any clinical trial. They have been urging the NCI and drug companies to open cancer clinical trials to people who have HIV ever since it became clear in the mid-1990s that these patients can live otherwise normal lives by taking the antiviral drugs.

"There was a time when there was a reason for exclusions, and that time is over," said Jeff Taylor, a California AIDS activist and founding director of the HIV & Aging Research Project – Palm Springs.

At the start of the AIDS epidemic, when patients' immune systems were devastated by the uncontrolled virus, toxic rounds of chemotherapy or radiation only added to the suffering. While the first antiviral drug combinations that emerged in the 1990s saved lives, they sometimes cross-reacted dangerously with cancer medications. But Taylor said that management of side effects has vastly improved since, and there are now nearly 30 drugs available to HIV patients.

Fred Hutch immunotherapy researcher Mac Cheever, MD, is director of the NCI-funded Cancer Immunotherapy Trials Network, which carried out the trial, and he is senior author of the JAMA Oncology paper. In his view, the exclusion from cancer trials of any patient with HIV is an anachronism and serves no purpose.

"If you read most protocols, they exclude patients with an active viral disease. HIV is an active viral disease. That might imply there was thought behind the exclusion, but I think it was just historically due to caution and a standard part of protocols," he said.

Cheever said the routine, blanket exclusion from cancer clinical trials of cancer patients with HIV is also rooted in fear that if anything goes wrong, it could jeopardize a company's chance of winning FDA approval for a new drug.

"Companies don't want to take a chance on their drug not working well or having more toxic events, until they get approval," Cheever said. "So, they are afraid and hesitant to include patients in a clinical trial. It might have been a rational decision, but it's very difficult on patients who have cancers and HIV."

There are no legal constraints on doctors prescribing a drug to an HIV-positive cancer patient once it is approved by the FDA. The problem caused by exclusions in clinical trials — for both the physician and the patient — is the lack of access to potentially beneficial therapies during the long period of testing, and a lack of data on which to base a decision to use the drug once it wins approval.

Ironically, one of the most difficult problems in clinical research is accruing enough patient volunteers to test a new drug. For those who have dire cancer diagnoses and are failing with approved therapies, participation in a clinical trial may be their only remaining option.

Uldrick noted that his own research showed it takes a median of 6.8 years for a successful drug to move from early clinical trials to FDA approval. During that time, only trial participants have that chance to try out unproven therapies well before they are available in the marketplace. It is an opportunity, of course, only if patients are allowed inside the door.

The study in patients with HIV and cancer was dedicated to Holbrook Kohrt, MD, PhD, a Stanford University clinical researcher who suggested the study and helped design the trial. As a youngster, Kohrt was diagnosed with hemophilia and attended camps for kids with the condition. Most of his camp friends died of AIDS complications after they were infected with HIV from tainted blood products. Kohrt was fortunate to be spared of HIV infection himself, and he built his career on the study of cancer and the immune system. Sadly, he passed away at the age of 38 from complications of hemophilia on Feb. 16, 2016, just two months before the first patients were enrolled in the trial.

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