

Popular cancer drug linked to often fatal brain virus

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The 57-year-old lawyer in New York had handily completed the New York Times' Saturday crossword puzzle - the hardest of the week - for years. But one Saturday morning, suddenly he couldn't retrieve the words to fill in the squares.

In Chicago, an 83-year-old woman began parroting the same phrases over and over. When her doctor asked her how she was, she replied, "I am fine. I am fine. I am fine."

The symptoms of the New York lawyer and the Chicago woman could have been mistaken for early dementia. But an MRI brain scan and biopsy revealed something surprising. It looked like their brains had been eaten away. A brain biopsy and a spinal tap confirmed the diagnosis of a swiftly moving and often fatal viral brain infection called progressive multifocal leukoencephalitis (PML) that attacks the brain's white matter. Both had lymphoma and had been taking the popular cancer drug rituximab (brand name Rituxan) before they developed the brain infection.

The two patients are part of a new study from the Northwestern University Feinberg School of Medicine RADAR project, led by Charles Bennett, M.D., that links rituximab to PML. Rituximab is the most important and widely used cancer drug for lymphoma. It is also approved for treatment of rheumatoid arthritis and is widely used off-label to treat multiple sclerosis, lupus erythematosus and autoimmune anemias.

Bennett reports on 57 cases from 1997 to 2008 in which patients with anemia, rheumatoid arthritis or lymphoma developed the fatal brain disease after taking rituximab. They died an average of two months after being diagnosed. The study was published in the May 14 issue of the journal Blood.

"Rituximab is one of the most prominent drugs in a new class called monoclonal antibodies. It's now the third monoclonal antibody that is associated with PML," said Bennett, the A.C. Buehler Professor in Economics and Aging at Northwestern's Feinberg School and a hematologist and oncologist at the Jesse Brown VA Medical Center in Chicago.

One of the other two drugs, Raptiva, was taken off the market in April of this year because of the PML risk. The other drug, Tysabri, was removed from the market for 1½ years because of similar concerns.

Bennett said the brain infection is often overlooked and undiagnosed because it is so subtle at first. "People may think it's early Alzheimer's disease or depression," he said. "Many of these patients have cancer and when they die, people assume it's the cancer that killed them."

It is not yet known how rituximab is connected to the brain virus and who may be at risk. Bennett notes that the best information on the frequency of PML is among patients with lupus with an estimated rate of 1 in 4,000 patients developing PML.

Monoclonal antibodies target one particular protein found on the surface of cells. In lymphoma, rituximab targets a protein called CD20 on the outside of B-cell lymphomas. The antibody binds to the protein, leading to the destruction of the cancerous cell.

"In non-Hodgkin's lymphoma, it turned out to be a home run," Bennett

said of the drug. "It's been a magic bullet."

But concerns about the drug's association with PML first surfaced in 2006 when two patients with lupus developed the illness after taking rituximab and other immunosuppressive treatments. In 2008, Bennett said, the manufacturers of the drug, Genentech and Biogen Idec, sent letters to doctors alerting them that a patient with rheumatoid arthritis who had been taking rituximab also died from the brain infection. The companies asked whether physicians had detected this illness among cancer patients who were taking the drug.

Bennett said it was known that a small number of patients with lymphoma get the infection regardless of the drug. "But it was atypical for lupus and [rheumatoid arthritis](#) patients to get it," he said. "It was especially unusual for patients with autoimmune anemia-like illnesses who have not received a large number of other drugs."

Then Steve Rosen, M.D., director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, noticed that the 83-year-old woman was repeating the same phrases over and over. After a brain biopsy identified the infection, Rosen alerted Bennett.

"I told him a serious abnormality was uncovered and the RADAR program needs to pursue it in the manner that he has investigated all other severe adverse drug problems," Rosen said.

Bennett's RADAR project (Research on Adverse Drug Events and Reports) is an international consortium of physicians that collaborate to identify adverse reactions to medications and devices.

Bennett met with Genentech executives, offering to help them gather what thus far had been elusive information on the drug's connection to the brain infection. Doctors had been reticent to report PML in their

patients who had been taking rituximab.

"It's a lot of work to produce these reports," Bennett explained about doctors' reticence.

To offset this concern, Bennett called 12 major cancer centers around the country, asked doctors to share their information and offered to produce the reports for them. He discovered an additional 22 cases beyond what had previously been reported.

The study results illustrate a need for caution in prescribing rituximab, Bennett said.

"The drug has tremendous usefulness in lymphoma, but as its use expands to diseases that are not cancer, we might have to reconsider the risk benefit," Bennett said. "Some cancer patients take this drug chronically for non-fatal chronic leukemia where the risk-benefit calculations differ from lymphoma."

The next step, Bennett said, is to determine the risk factors for the disease in people who take rituximab.

"We need to learn more about this, " he said. "People have to think about the pros and cons in settings where it is being used for nonmalignant diseases. People have been lulled into a false sense of security that this drug is harmless and that it only does good things. No drug is perfect."

If people on rituximab develop any strange neurological symptoms such as forgetfulness, disorientation or mood changes, their doctors should be alerted, Bennett said.

Source: Northwestern University ([news](#) : [web](#))

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