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Drug for anemic cancer patients raises risk of death

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Millions of cancer patients take drugs to boost their red blood cells and health when they become anemic after chemotherapy. But a new study by Northwestern University's Feinberg School of Medicine shows these drugs, called erythropoiesis-stimulating agents (ESAs), actually raise patients' risk of death, possibly by stimulating the growth of cancer cells.

A meta-analysis of 51 trials with 13,613 patients revealed a 10 percent increased risk of death among cancer patients taking ESAs compared to patients who did not take them. The study, lead by Charles Bennett, M.D., the A.C. Buehler Professor in Economics and Aging at the Feinberg School, will be published in the Journal of the American Medical Association Wednesday, February 27.

The Northwestern study is the first to demonstrate a quantifiable increased risk of death from EPAs and is based on the largest number of trials ever examined for this purpose.

"The FDA says if you use the drug in moderation, it should be safe," Bennett said. "But our findings, in conjunction with basic science studies, raise the concern that the drug may be stimulating cancer and shortening cancer patients' survival."

“It’s troubling that 15 years after the drug came out, we finally came to this realization," said Bennett, who also is a hematologist and oncologist at Northwestern Memorial Hospital and the Jesse Brown VA Medical Center.

The JAMA paper is an update of a poster presentation Bennett made to the American Society of Clinical Oncology in June 2007.

One of the study's co-authors, Stephen Lai, M.D., assistant professor at the University of Pittsburgh Medical Center, tested the response of cancer cells to an ESA in the laboratory. Lai, a head and neck surgeon, saw a significant effect when he added an ESA called erythropoietin to head and neck cancer cells in tissue culture.

"We saw a dramatic change," Lai said. "Adding 'epo' (erythropoietin) to the cells increased their ability to migrate or invade. Our basic science findings and the clinical trial results suggest that giving cancer patients 'epo' for their anemia may actually cause their tumors to progress."

Lai's basic science study is part of a growing body of studies that demonstrate erythropoietin expression and function in a variety of human cancers as presented at a National Cancer Institute workshop on erythropoietin and tumor progression December 2007 in Bethesda, Md.

The FDA approved the ESAs erythropoietin and darbepoetin in 2003 as a treatment for anemic cancer patients to avoid blood transfusions. However, evidence linking these drugs to a higher risk of death has been mounting. In March 2007, the FDA issued a public health advisory on EPAs, warning of an increased risk of serious and life-threatening side effects.

Ironically, Bennett noted, "The later clinical trials were conducted to see if these drugs help people live longer. But, it turns out, this is not the case."

ESAs produced up to $6 billion in cancer-anemia related sales last year for pharmaceutical firms, Bennett said, and represented Medicare's largest pharmaceutical expenditure.

Bennett began investigating these drugs when the study's senior author, Michael Henke, M.D., professor of medicine in radiation oncology at the University of Freiburg in Germany, first raised an alarm in 2003. For the new study, Bennett and his co-authors updated a 2006 analysis by the Cochrane Collaboration with more recent statistics from 13 additional Phase III trials. The 2006 Cochrane study did not show an increased risk of death, Bennett said.

"This is why it's important to continuously look at the data," Bennett said. "You can't let it fall by the wayside. Just a year out of date is not acceptable. Importantly, the more recent clinical studies were larger and addressed the issue of survival."

The Northwestern study also confirmed a previously known 57 percent increased risk of blood clots in the legs or lungs for cancer patients receiving ESAs. But the higher blood clot risk did not explain the 10 percent increased risk of death shown in his study, Bennett said.

"We know that ESA's may prevent a blood transfusion, but if I had cancer and I needed a blood transfusion, I would be much more conservative about taking ESAs," Bennett said. "The current FDA recommendation is these drugs are safe for cancer patients as long their hemoglobin levels aren't raised too high. Our data do not support that."

Lai cautioned that various solid tumors such as breast cancer, colon cancer and melanoma may react differently to ESAs. "The exact effect and size of that effect may be different depending upon the type of tumor. Additional research is clearly necessary, and we have to be careful about generalizing these results before further research is conducted," he said.

On March 13, the FDA's Oncologic Drugs Advisory Committee will meet in Gaithersburg, Md. to discuss the cumulative data, including the

recent study results, regarding the use of ESAs for cancer patients, Bennett said.

Source: Northwestern University