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Cancer Drugs That Block Blood Vessel Growth From Inside Cells May Lead to Serious Health Problems in the Long Term

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Angiogenesis inhibitors, drugs that block a tumor's development of an independent blood supply, have been touted as effective cancer fighters that result in fewer side effects than traditional chemotherapy. However, a new study by researchers at UCLA's Jonsson Cancer Center has shown that one method of blocking blood-supply development could result in serious and potentially deadly side effects.

Several newly developed angiogenesis inhibitors work by blocking vascular endothelial growth factor (VEGF), an important signaling protein that spurs the growth of new blood vessels. Avastin, an angiogenesis inhibitor approved by the Food and Drug Administration for colon and lung cancers, inhibits angiogenesis by blocking VEGF signaling from outside the cell. UCLA researchers wanted to know what happened when VEGF signaling was blocked from within endothelial cells, a mechanism used by some small-molecule drugs currently being tested in late-phase clinical trials.

The result was unexpected and sobering. More than half of the mice in the study suffered heart attacks and fatal strokes, while those that remained alive developed serious systemic vascular illness, said Luisa Iruela-Arispe, a professor of molecular, cell and developmental biology and director of the Cancer Cell Biology program at UCLA's Jonsson Cancer Center.

The study appears Aug. 24 in the prestigious peer-reviewed journal Cell.

"This was an extremely surprising result," said Iruela-Arispe, past president of the North American Vascular Biology Organization and a national expert on angiogenesis. "I think this study is cause for some caution in the use of angiogenesis inhibitors in patients for very long periods of time and in particular for use of those inhibitors that block VEGF signaling from inside the cell."

About 5 percent of patients taking Avastin develop blood clot-related side effects, Iruela-Arispe said. But because Avastin was approved only three years ago, it is unclear what side effects may occur when patients remain on the drug for many years, she said.

In the three-year study, Iruela-Arispe created mice that were missing VEGF in the endothelial cells, the cells that line the inside of blood vessels and form an interface between circulating blood and the vessel wall. Endothelial cells line the circulatory system from the heart to the smallest capillary and reduce friction in the flow of blood. Iruela-Arispe and her team did not expect to see much of an effect because the amount of VEGF made inside endothelial cells is miniscule compared with the levels of VEGF created outside the cells.

However, 55 percent of the mice in the study died by 25 weeks of age, the equivalent of age 30 in humans. The mice that were followed into old age were very ill.

"Some side effects have already been identified in people taking angiogenesis inhibitors," Iruela-Arispe said. "And they've been along the lines of what we're seeing in the lab."

Iruela-Arispe and her team were surprised that the higher levels of VEGF found outside the endothelial cells did not compensate for the

absence of the very tiny amounts inside the cells. The miniscule amount of VEGF missing had "a tremendous biological significance," she said.

"Clearly there is signaling from inside the cell that is different from signaling initiated outside the cell," Iruela-Arispe said. "When there is no VEGF signaling inside the cell, the endothelial cells die. The intracellular part of the VEGF signaling loop is required for cell survival. This is the first demonstration that intracellular signaling is an important event."

It had been unclear why some patients on angiogenesis inhibitors developed problems with blood clots. Iruela-Arispe said her study sheds light on one possible cause.

"There is enough smoke in the sky here to make me feel there may be a fire," she said. "I believe the survival function of VEGF signaling is mediated from both outside and inside the cell. When we block it from the inside, the outside signaling cannot compensate. But when we block it from the outside, maybe the inside signaling can compensate. That would explain the lesser side effects found when using drugs such as Avastin, which block the extracellular signaling."

Iruela-Arispe believes angiogenesis inhibitors will continue to be effective weapons in the cancer arsenal. However, a more targeted approach to drug delivery should be explored. Avastin, like most angiogenesis inhibitors, is infused systemically now. If the drugs could be targeted more directly to the new vessels being formed by the tumor, they might not result in the side effects seen now.

Source: UCLA