Metformin Lowers Breast Cancer Tumor Markers in Some Women

REUTERS HEALTH INFORMATION

By James E. Barone MD

NEW YORK (Reuters Health) May 17 - Italian investigators say metformin may lower the levels of Ki-67, a breast cancer tumor marker, in women with insulin resistance.

"Reducing levels of the tumor cell proliferation marker Ki-67 improves the outcome of women with breast cancer. Three studies have shown this including one from our group," said Dr. Andrea DeCensi, who led the study, in an email to Reuters Health. Those studies all involved hormonal therapy.

But the main goal of Dr. DeCensi's latest study was to look at the effect of metformin on Ki-67 levels in a mixed population of women, not just in those with insulin resistance. And in the overall cohort, the effect wasn't statistically significant.

That led at least one outside expert to suggest that at best, the results raise new questions.

Dr. DeCensi, from Galliera Hospital in Genoa, and his colleagues published their findings online May 7th in the Journal of Clinical Oncology.

Their randomized, double-blind trial took advantage of the window of opportunity between the biopsy of the tumor and the definitive surgery. For those four weeks, they treated 200 nondiabetic women with either metformin or placebo, obtaining tissue for analysis of Ki-67 levels before and after treatment.

All subjects were evaluated for insulin resistance by the homeostasis model assessment (HOMA) index. Subgroup analysis was planned for HOMA index, dichotomized as lower or higher than 2.8, and estrogen receptor (ER) status.

Compared to placebo, metformin did not significantly change Ki-67 levels, but in the subgroup of patients with high HOMA indices (i.e., those with insulin resistance), Ki-67 was reduced by 10.5%, a marginally significant difference, p=0.045, which could have been confounded by the assessment of multiple variables.

In patients with low HOMA indices, Ki-67 rose by 11.1%, which was not significant.

Ki-67 levels were not affected by ER status, but the unexpected finding that 85% of the subjects had ER-positive tumors meant the study did not have the power to discriminate this.

Dr. DeCensi said, "The study is negative for the primary hypothesis that metformin lowers Ki-67 in all women with breast cancer. This assumption was wrong in principle as metformin is a host-targeted drug, which is not effective in women who are not insulin resistant or overweight."

A physician not part of the study group, Dr. Pamela J. Goodwin, who holds the Marvelle Koffler Chair in Breast Research at the University of Toronto, spoke to Reuters Health by telephone. She agreed with Dr. DeCensi that the study was a negative one.

Even if the secondary analyses were preplanned, Dr. Goodwin said, "That is not the ideal situation. There was no adjustment of the p-values for multiple analyses. I view this as a negative study that raises some hypotheses that require replication."

She was also concerned that the metformin was stopped almost three days before the surgery, in accordance with instructions from the U.S. Food and Drug Administration for minimizing the risk of lactic acidosis. Since its half-life is 18 hours, the drug's effect may have worn off, she said.

Dr. DeCensi's group will next be looking at three areas: separating responders from non responders based on host characteristics and blood or tissue biomarkers, characterizing the mechanism of action of metformin in humans using genomic profile and mutational analyses, and determining whether metformin has preventive potential through modulation of tumor adjacent dysplasia and distant hyperplasia.

Dr. Goodwin's own studies have shown that insulin is probably what promotes tumor growth, not sugar itself, and high insulin levels indicate a worse prognosis. She said, "Metformin reduces insulin levels in non-diabetic patients, and six months of metformin therapy shows that it works the same for non-diabetic women, obese or not."

Whether the current study helps clarify the relationship between diabetes and cancer is not clear. According to Dr. DeCensi, "The study supports the concept that inhibition of insulin has anti-tumor effects in humans. So the relationship between high glucose diet, diabetes and certain cancers is strengthened."

But Dr. Goodwin is not convinced. "Perhaps, but these women did not have diabetes so we need to be careful," she said.

Dr. Goodwin notes that a large international trial of the effect of metformin on breast cancer outcomes is underway and has accrued 2,000 of the planned 3,500 subjects. Its results should be available by 2016.

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