Bisphosphonate treatment fails to improve outcomes for women with chemoresistant breast cancer

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Treatment with the bisphosphonate zoledronate did not improve outcomes for women with chemoresistant breast cancer, according to initial results of a phase III clinical trial presented here at the 2013 San Antonio Breast Cancer Symposium, held Dec. 10-14.

Many patients with breast cancer are treated with chemotherapy prior to surgery. In some patients who receive this form of treatment, which is called neoadjuvant therapy, no residual invasive cancer can be detected in breast tissue samples and lymph nodes removed during surgery. Patients with residual disease are considered to have breast cancer that is resistant to chemotherapy, and emerging data indicate that they experience poorer long-term outcomes compared with women who respond completely to neoadjuvant therapy.

"Because patients with residual disease after neoadjuvant chemotherapy are considered to have chemoresistant breast cancer, they have few postsurgery treatment options," said Gunter von Minckwitz, M.D., Ph.D., chairman of the German Breast Group in Neu-Isenburg, Germany. "We evaluated a new postsurgery treatment for these patients, the bisphosphonate zoledronate, in a phase III clinical trial.

"We are disappointed to report that zoledronate had no effect on event-free survival. That is, it had no effect on the number of patients who had disease relapse, developed a new cancer, or died.Although the results are completely negative, we hope that our experience running the first phase III clinical trial to test a treatment in women who had not had a complete response to neoadjuvant therapy will inform future post-neoadjuvant phase III clinical trials," added von Minckwitz, who is also professor of gynecology at the University of Frankfurt. "We experienced a number of challenges while conducting this study, and are sharing what we have learned with other researchers running, or thinking of running, these extremely complicated clinical trials."

The phase III clinical trial conducted by von Minckwitz and colleagues is referred to as the NATAN study, or NeoAdjuvant Trial Add-oN. From February 2005 to May 2009, 654 patients who had residual invasive disease detected in breast tissue samples and/or lymph nodes removed during surgery after having received neoadjuvant chemotherapy were enrolled in the study. After surgery, patients were randomly assigned to either zoledronate for five years or no investigational postsurgery treatment. Those with hormone receptor-positive disease also received antihormone treatment for five years. From 2007, patients with HER2-positive disease also received trastuzumab for one year.

During a median follow-up of 48 months, 154 events were reported, with no difference observed between the two groups in an interim analysis for futility.

According to von Minckwitz, they had expected twice the number of events at this stage of follow-up when planning the study, so the time to reporting results was twice as long as they had anticipated.

He also explained that a large number of patients with hormone receptor-positive disease enrolled in the study, 82 percent of participants had this form of breast cancer, and that the effects of different treatments on outcome are often only detectable five or more years later for patients with this disease. As a result, the researchers will keep following participants in the NATAN study, "but I am not hopeful of seeing zoledronate improve

outcomes," said von Minckwitz.

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