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Gene alterations associated with response to anthracycline therapy for breast cancer

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Alterations in the topoisomerase II alpha (*TOP2A*) gene were associated with better patient outcomes following anthracycline-based therapy compared with non-anthracycline-based regimens, according to a study in the April 28 online issue of the *Journal of the National Cancer Institute.* The increased responsiveness is similar to what is seen in patients whose tumors carry an amplification of the *HER*2 gene.

Several studies have shown that women whose tumors have amplified *HER2* derive benefit from regimens that include anthracyclines, such as epirubicin and doxorubicin, while patients whose tumors lack such alteration do not. Scientists have hypothesized that this difference could be due to alterations in the *TOP2A* gene, which resides adjacent to *HER2* on the chromosome and is often included in the stretch of amplified DNA. *TOP2A* is a major target of anthracycline.

To determine whether the difference in responsiveness is due to *TOP2A*, Kathleen I. Pritchard, M.D., of the University of Toronto, and colleagues re-analyzed data from the randomized Mammary 5 trial, conducted by the National Cancer Institute of Canada Clinical Trials Group. This trial compared an anthracycline-containing regimen (cyclophosphamide, epirubicin, and 5-fluorouracil; CEF) with a non-anthracycline-containing regimen (cyclophosphamide, methotrexate, and 5-fluorouracil; CMF) in 710 breast cancer patients. The investigators were able to analyze tumor samples from 438 patients for alteration of the *TOP2A* gene.

Women whose tumors carried *TOP2A* gene alterations had 65 percent

better relative relapse-free survival and 67 percent better relative overall survival when treated with CEF compared with CMF. The differences were statistically significant. By contrast, women whose tumors were *TOP2A*-normal had a similar response to the two regimens. The added benefit detected for the women with *TOP2A*-altered tumors when treated with anthracycline-based therapy is similar to the benefit the researchers detected in women with *HER2*-positive tumors.

The investigators conclude that *TOP2A* gene alteration is associated with increased benefit from an anthracycline-containing regimen compared with *TOP2A*-normal tumors. However, they add that the sample size was too small to determine whether this effect was independent of *HER2*.

Patients whose tumors are normal for *TOP2A* and *HER2* do not appear to derive additional benefit from the anthracycline-based regimen and therefore could be treated with less toxic regimens, such as CMF, according to the authors. "Our data suggest that measurements of *TOP2A* alteration and *HER2* ampli¬fication appear to have similar value in guiding the selection of anthracycline-containing regimens," they conclude.

In an accompanying editorial, Dennis J. Slamon, M.D., Ph.D., of the University of California School of Medicine at Los Angeles, and Michael F. Press, Ph.D., of the University of Southern California Keck School of Medicine in Los Angeles, agree that women whose tumors are *TOP2A*- and *HER2*-normal should not receive anthracycline-based therapy: "Currently, the overwhelming bulk of the published and/or reported data indicate that *TOP2A* alterations are the important predictive factors for determining the likelihood of incremental benefits from treating breast cancer patients with anthracyclines in the adjuvant setting," the editorialists write. "These data also show that *TOP2A* alterations most often occur in the context of *HER2* amplification."

More information:

Article: O'Malley et al. Topoisomerase II Alpha and Responsiveness of Breast Cancer to Adjuvant Chemotherapy, J Natl Cancer Inst 2009, 101: 644-650

Editorial: Slamon D. and Press M., Alterations in the TOP2A and HER2 Genes: Association with Adjuvant Anthracycline Sensitivity in Human Breast Cancers, J Natl Cancer Inst 2009, 101: 615-618

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