Jury Out on Antidepressant Use With Tamoxifen

BY KERRI WACHTER

ORLANDO — There's still no clear answer to whether CYP2D6 inhibitors—including some leading antidepressants—reduce the effectiveness of tamoxifen and increase the risk of breast cancer recurrence, based on the conflicting results of two retrospective database studies presented at the annual meeting of the American Society of Clinical Oncology.

Ronald Aubert, Ph.D., and his colleagues found that concomitant use of a CYP2D6 inhibitor increased the risk of recurrence at 2 years among 1,659 women identified through a large combined U.S. medical and pharmacy claims database. The increased risk was even greater for drugs deemed to be moderate or potent CYP2D6 inhibitors.

Dr. Vincent Dezentjé and his colleagues, however, found no increased risk in a study of 1,962 women identified through three large Dutch databases of hospital admissions, pharmacy claims, and pathologic data. Even when they looked at drugs deemed to be strong CYP2D6 inhibitors, the Dutch researchers saw no greater risk of recurrence.

"Additional studies that incorporate both genetic variants and use of inhibitors are required," said Dr. Vered Stearns of Johns Hopkins University in Baltimore in a discussion of the studies. Until further data are available, "concomitant use of CYP2D6 inhibitors should be limited," and noninhibitor alternative drugs should be considered.

Hepatic cytochrome P450 2D6 (CYP2D6) is key to the metabolic activation of tamoxifen to its active metabolite, endoxifen. Several previous studies have shown that women receiving tamoxifen have lower levels of endoxifen and are at greater risk of breast cancer recurrence if they have reduced-function CYP2D6 polymorphisms (poor metabolizers). Likewise, previous small studies with CYP2D6 inhibitors and tamoxifen have shown reductions in endoxifen, but have not clearly delineated their impact on breast cancer recurrence.

In their retrospective cohort analysis, Dr. Aubert and his colleagues mined medical and pharmacy claims from the 10 million member integrated database of Medco Health Solutions Inc. They used ICD-9 and CPT-4 codes to define the clinical end points. Dr. Aubert said he and several of his coinvestigators are employed by Medco Health Solutions.

Even concomitant use of drugs deemed to be strong inhibitors didn't increase breast cancer recurrence.

DR. DEZENTJÉ

The study population included women who initiated tamoxifen therapy between July 1, 2003, and Dec. 31, 2005. In all, 1,659 women met the criteria for tamoxifen adherence and breast cancer diagnosis. Of these, 945 women had no CYP2D6 inhibitor therapy, 359 women were considered to be exposed to a moderate or potent CYP2D6 inhibitor while on tamoxifen, and 355 women had either no overlap of CYP2D6 inhibitor and tamoxifen therapy or were on CYP2D6 inhibitors that were considered to be weak. Follow-up measurement started 6 months after the initiation of therapy and continued through Dec. 31, 2007.

"When we looked at the distribution of the types of CYP2D6 inhibitors, 79% were antidepressants, with the majority of those being an SSRI (52%)," said Dr. Aubert. In addition, 6% of women were on a serotonin-norepinephrine reuptake inhibitor, 34% were on some other type of antidepressant, 12% were on an antifungal, and 18% were on seven other drugs in unique classes. The mean duration of overlap with tamoxifen was 340 days; the median was 287 days.

Women on CYP2D6 inhibitors had an almost doubled incidence of breast cancer recurrence. For women not on a CYP2D6 inhibitor, the incidence was 7.5% vs. 13.9% in women on a moderate or potent CYP2D6 inhibitor (hazard ratio, 1.92; *P* less than .001).

"Moderate to severe CYP2D6 inhibitors used concomitantly with tamoxifen were associated with a 92% greater risk of breast cancer recurrence vs. tamoxifen alone," said Dr. Aubert. Moderate to potent CYP2D6 inhibitor SSRIs (fluoxetine, paroxetine, and sertraline) were associated with a 120% increase in the risk of breast cancer recurrence, whereas weak CYP2D6 inhibitor SSRIs (citalopram, escitalopram, and fluvoxamine) were not associated with an increased risk.

Dr. Dezentjé of Leiden (the Netherlands) University Medical Center and his coinvestigators also performed a retrospective follow-up study. They used three large linked databases: a pharmacy database (PHARMO), a pathology database (PALGA), and a hospital admissions database (Dutch Medical Register) to look at nine CYP2D6 inhibitors: bupropion, paroxetine, fluoxetine, quinidine, duloxetine, terbinafine, amiodarone, cimetidine, and sertraline.

Patients were included if they had a pathology report of a breast cancer resection specimen between 1994 and 2006 and had used tamoxifen in the same period. In all, 3,147 patients were identified with primary breast cancer, of which 1,962 were eligible for this analysis. Most (89%) were on tamoxifen alone, leaving 213 women on tamoxifen and a CYP2D6 inhibitor. Only 150 women met the criteria (at least 60 days) for concomitant use, however, and about 70% were on either paroxetine or fluoxetine.

In a univariate Cox regression analysis, the researchers found no difference in event-free time between women who did not use CYP2D6 inhibitors and women who used concomitant tamoxifen and CYP2D6 inhibitors (HR, 0.95; $P = .73$). "Even if we restricted our analysis to strong inhibitors, we could not find any difference," Dr. Dezentjé said. Dr. Dezentjé and his coauthors reported that they have no relevant financial relationships.

Dr. Stearns noted that both of the studies have several limitations. Both were retrospective studies with relatively small sample sizes and limited follow-up. "In addition, there may be incomplete accountability for recurrences, as those were determined by hospital admission. As we know, breast cancer is very much an outpatient disease." Moreover, the reason for inhibitor use is not known in either study.

In the Medco cohort, claims data are limited, and women with early recurrences or with low medication possession rates were excluded. In the European cohort, "the magnitude of the effect may have been diluted by short concomitant medication use," she said.

Dr. Stearns reported that she had significant financial relationships with several pharmaceutical companies. ■

Studies Raise Questions About Partial-Breast Irradiation

BY PATRICE WENDLING

ORLANDO — Whole-breast irradiation resulted in no overall survival benefit over partial-breast irradiation in women with early breast cancer in a meta-analysis of three randomized clinical trials.

There were no statistically significant differences between the two therapies with regard to death (odds ratio, 0.91; $P = .550$), distant metastasis (OR, 0.74; $P = .120$), or supraclavicular recurrences (OR, 1.41; $P = .560$), according to a late-breaking abstract at the annual meeting of the American Society of Clinical Oncology.

Women treated with partial-breast irradiation were twice as likely to have local recurrence (OR, 2.15; $P = .001$), however, and three times more likely to have axillary recurrence (OR, 3.43; *P* less than .0001).

"Partial-breast irradiation may be safe and feasible for women with early-stage breast cancer because it does not jeopardize patient survival or the risk of metastasis," coauthor Dr. Davide Mauri of the General Hospital of Lamia (Greece) told reporters at a press briefing. "Locoregional issues need to be further addressed."

The findings are reassuring in terms of equivalent overall survival and reduction in risk of metastasis, but are not enough to change practice, said Dr. Jennifer Obel, who moderated the briefing. "Before we say from a meta-analysis that this should be the next standard of care for treating women with early-stage breast cancer, there are many randomized studies sponsored by major cooperative groups … that are forthcoming in the next couple of years and we should await those before we make our decision," said Dr. Obel of NorthShore University HealthSystem in Chicago's Northern suburbs.

Two trials that could provide additional insights are the TARGIT (Targeted Intraoperative Radiation Therapy) trial in Europe and the National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology Group 0413 trial in the United States, Dr. Obel said in an interview.

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DR. OBEL

The U.S. phase III trial will compare the effectiveness of the two irradiation strategies in 4,300 women after lumpectomy for early-stage breast cancer. It will use three technologies: high-dose-rate multicatheter brachytherapy, high-dose-rate single-catheter balloon brachytherapy (Mammosite), and three-dimensional conformal external beam radiation therapy.

"It's one of the largest trials of its size that will be looking at whole-breast irradiation compared to various techniques of partial-breast irradiation," she said. "These are the some of the most patient-friendly techniques." She acknowledged that partial-breast irradiation improves patient compliance because it is typically given over 5 days, compared with 5 weeks or more for whole-breast radiation.

Dr. Mauri agreed that ongoing trials will further clarify whether partial-breast irradiation offers high efficacy with better cosmetic outcomes.

He suggested that technique may have played a role in biasing the locoregional recurrence results in the meta-analysis. Two of the three studies used a standardized field of radiation, irrespective of tumor size, which could have led to areas of disease being missed and increasing local recurrence. In addition, one of the studies included women with extremely large tumors as well as node-positive patients. "I think that this explanation makes this finding of increased local recurrence less concerning."

The meta-analysis included a total of 1,140 women (575 randomized to whole-breast radiation therapy and 565 to partial-breast irradiation). Median survival follow-up ranged from 5 to 8 years. The investigators, led by Dr. Antonis Valachis of the University Hospital of Heraklion in Crete (Greece), disclosed no conflicts of interest. ■