SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio | AACR American Association for Cancer Research | Baylor College of Medicine

2018 | DECEMBER 4-8

HENRY B. GONZALEZ CONVENTION CENTER, SAN ANTONIO, TEXAS, USA

LOW-DOSE TAMOXIFEN REDUCES BREAST INTRAEPITHELIAL NEOPLASIA RECURRENCE

Low-dose tamoxifen significantly reduces the recurrence of breast intraepithelial neoplasia, according to a randomized phase III trial presented by Dr. Andrea DeCensi of Genoa, Italy.

Intraepithelial neoplasia accounts for approximately 20% of all breast neoplasms, including atypical ductal hyperplasia, ductal carcinoma in situ, and lobular carcinoma in situ, according to Dr. DeCensi. Standard treatment of these patients includes surgery and 20 mg/day of tamoxifen (with or without subsequent radiotherapy).

"Tamoxifen is very effective and has saved millions of lives, but its side effects present a barrier for use in primary prevention, and its minimal active dose has never been carefully assessed," said Dr. DeCensi.

A previous randomized postsurgical trial showed that low-dose tamoxifen (1- and 5-mg daily doses) was noninferior to 20 mg/day in decreasing proliferation biomarker Ki67. Based on this type of previous research, Dr. DeCensi and his colleagues hypothesized that the use of 5 mg/day of tamoxifen for 3 years would be just as effective and less toxic than the conventional dose of 20 mg/day.

Dr. DeCensi's group conducted their study at 14 centers in Italy. They randomized a total of 500 women to either 5 mg/day of tamoxifen or placebo for 3 years. The women were <75 years old with atypical ductal carcinoma, lobular carcinoma, or ductal carcinoma in situ that was estrogen receptor-positive or of unknown hormone receptor status. Median follow-up was 5.1 years.

Dr. DeCensi said that the lower dose of tamoxifen halved the recurrence of breast intraepithelial neoplasia. Investigators observed a 52% decrease in the risk for recurrence with the 5-mg dose. Among patients who received the low tamoxifen dose, there were 14 breast cancer events, compared to 28 breast cancer events among women who were randomized to placebo.

Also noted was a significant decrease in contralateral breast cancer events in the low-dose tamoxifen group (12 vs 3), suggesting a strong preventive potential. "However, this analysis is only based on 15 events, so we need to be cautious," Dr. DeCensi said.

The known side effects and adverse events associated with tamoxifen use include increased risk for endometrial cancer, venous thromboembolism, and menopausal symptoms.

Based on patient self-reports, study investigators determined that there was a borderline statistically significant increase in hot flashes (but not significant difference in the daily hot flash score) among patients who received tamoxifen, compared to those assigned to placebo. "About one extra hot flash per day," Dr. DeCensi said.

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ISSUE 3 AT A GLANCE

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ISSUE 3 UPDATES

FRIDAY, DECEMBER 7

An addition has been made to the list of panelists for this session.

SPECIAL SESSION:
Stars at Night Ballroom 3&4
3rd Level
6:00 PM– 7:00 PM

View from the Trenches: What Will You Do On Monday Morning?

Ruth O'Regan, MD
University of Wisconsin Carbone Cancer Center
Madison, WI

WITHDRAWN ABSTRACTS

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- P4-07-02
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*AT PRESS TIME

There was no difference in vaginal dryness, pain during intercourse, and musculoskeletal pain between the groups.

The rate of endometrial cancer and deep vein thrombosis or pulmonary embolism with the 5-mg dose of tamoxifen was not different from placebo, and was 2.5 times lower than that with the 20-mg dose. One case of endometrial cancer in the tamoxifen treatment group was reported, but none in the placebo arm. Dr. DeCensi mentioned that 2.7 cases of endometrial cancer would have been expected in a 3-year trial using the standard tamoxifen dose of 20 mg.

"Our results have external validity and are generalizable. Our findings are applicable in clinical practice from tomorrow," Dr. DeCensi concluded.

ALPELISIB AND FULVESTRANT PROLONGS PROGRESSION-FREE SURVIVAL IN PIK3CA-MUTANT, ESTROGEN RECEPTOR-POSITIVE ADVANCED BREAST CANCER

The combination of alpelisib and fulvestrant prolongs progression-free survival in patients with PIK3CA-mutant, estrogen receptor-positive advanced breast cancer who progressed on or after prior aromatase inhibitor-based therapy, according to results of the randomized phase III SOLAR-1 trial, presented Thursday morning by Dr. Dejan Juric of Massachusetts General Hospital in Boston.

Approximately 40% of estrogen receptor-positive breast cancers harbor mutations in the PIK3CA gene, resulting in tumor growth and treatment resistance. "This alteration is the most common actionable alteration in ER+ breast cancer," said Dr. Juric.

Investigators randomized a total of 572 patients with estrogen receptor-positive advanced breast cancer to alpelisib (an investigational α-specific PI3K inhibitor) and fulvestrant, or placebo and fulvestrant. Patients were divided into two cohorts based on whether they had PIK3CA-mutant disease. Progression-free survival in patients with PIK3CA-mutant disease was the primary endpoint.

The study met its primary endpoint with statistical significance. Dr. Juric and his colleagues saw a clinically meaningful prolongation in progression-free survival with the addition of alpelisib to fulvestrant (from 5.7 months to 11 months). He also noted that 75.9% of patients in the alpelisib arm experienced at least some tumor shrinkage, compared with 43.9% of patients in the placebo arm.

In addition to tissue-based biopsy, investigators conducted a polymerase chain reaction-based circulating tumor DNA analysis to assess progression-free survival by PIK3CA mutation status. The retrospective analysis found that the combination of alpelisib and fulvestrant resulted in median progression-free survival of 10.9 months, compared to 3.7 months with placebo and fulvestrant. "This analysis clearly illustrates the potential clinical value of this easily accessible biomarker," said Dr. Juric.

Data about overall survival in patients with a PIK3CA mutation were immature. However, Dr. Juric acknowledged a "positive trend." Median overall survival had not been reached in the alpelisib and fulvestrant arm. "Two additional overall survival analyses will shed a lot more light on the potential benefit of this combination, and they will be presented once they are mature," he said.

The most common adverse events seen with the alpelisib and fulvestrant combination were hyperglycemia, diarrhea, nausea, and skin rash.

Grade 3 or higher hyperglycemia, an adverse event "inextricably linked with the on-target activity of alpelisib and insulin resistance," developed in slightly over one-third of patients. These patients were easily identified and managed with dose interruptions, dose adjustments, or early initiation of insulin sensitizers, such as metformin.

Among patients in the alpelisib arm, 56% were classified as prediabetic and 4% as diabetic based on baseline fasting plasma glucose and hemoglobin A1C levels. These patients experienced spikes in fasting plasma glucose during the first cycle (first 2 weeks) of alpelisib treatment, but glucose levels fell closer to baseline by the start of the second cycle of treatment.

"It's important that some of these phase I participants (enrolled over 6 years ago) are still under study, and are able to witness the results of this trial and the progress of the drug's development," Dr. Juric concluded.

PARTIAL BREAST IRRADIATION VERSUS WHOLE BREAST IRRADIATION FOR CONTROLLING IPSILATERAL BREAST TUMOR RECURRENCE

Partial breast irradiation (PBI) delivered over a period of 5 to 7 weeks did not meet non-inferiority criteria compared with whole breast irradiation (WBI) for controlling local in-breast tumor recurrence (IBTR), Frank A. Vicini, MD, reported here on Thursday.

In a study of 4,216 patients with ductal carcinoma in situ (DCIS) or invasive stage pN0 or pN1 breast cancer, 95.9% of women who underwent WBI were free of IBTR at 10 years, compared with 95.2% of women who had undergone PBI, a statistically insignificant difference, said Dr. Vicini, of the MHP Radiation Oncology Institute in Pontiac, Michigan.

However, Dr. Vicini also pointed out that the absolute difference between the groups in the 10-year rate of IBTR was less than 1%: 4.1% versus 4.9%, and "the absolute difference in 10-year cumulative incidence of IBTR between PBI and WBI was only 0.7% (4.6% vs 3.9%)." Similarly, the risk of a relapse-free interval (RFI) event was 1.6% higher for patients in the PBI group, which was statistically significant, but here again, he said, the absolute differences were small.

Because these differences were so small, there may still be a role for PBI for women who want a better cosmetic result after undergoing breast-conserving surgery, Dr. Vicini said.

The findings come from a study known as NSABP B-39/RTOG 0413, which enrolled pre- and post-menopausal women whose tumors could be hormone receptor-positive or -negative. To be eligible for the study, patients had to have undergone lumpectomy, have histologically free margins, and no more than 3 positive axillary nodes.

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Essentially, Dr. Vicini explained, the study's primary aim "was to determine if PBI provides equivalent local tumor control post-lumpectomy compared to WBI in patients with early-stage breast cancer." Its primary endpoint was IBTR (invasive or DCIS) as a first recurrence. The investigators also looked at three secondary endpoints: distant disease-free interval, recurrence-free interval, and overall survival.

Study participants had a median age of 54 years. They were stratified according to disease stage, menopausal status, hormone receptor status, and intent to receive chemotherapy. Women randomized to the WBI group (n=2109) then underwent irradiation with a total dose of about 50 Gy in 25 or 28 fractions, following adjuvant chemotherapy. PBI consisted of 10 fractions of 3.4-3.85 Gy, administered twice daily over 5 to 10 days with either brachytherapy or external beam radiation. Following treatment each patient had follow-up appointments every 6 months for 5 years, and then annually for the remainder of the study. Patients were enrolled between March 21, 2005, and April 16, 2013, with a median follow-up of 10.2 years as of July 31, 2018.

The primary analysis was conducted in the form of an equivalence test, with a 50% increase in the hazard ratio (HR) chosen as the acceptable margin. That is, for PBI and WBI to be deemed equivalent with respect to IBTR risk, the 90% confidence interval for the observed HR had to lie between 0.667 and 1.5, Dr. Vicini explained.

There were a total of 161 IBTRs as first events, of which 90 occurred among patients in the PBI group and 71 in the WBI group. This yielded a hazard ratio of 1.22, with 90% confidence intervals of 0.94-1.58, requiring the investigators to conclude that "PBI did not meet the criteria for equivalence to WBI in controlling IBTR," according to the standards established at the outset of the study, Dr. Vicini said, despite the small absolute difference in the cumulative incidence of IBTR between the groups.

Of the 71 recurrences among women in the WBI group, 46 occurred at the site of the primary tumor and 25 occurred elsewhere in the breast. Women in the PBI group had 39 recurrences at the site of the primary tumor and 51 elsewhere in the breast. There were no statistically significant differences between treatment groups with respect to recurrence-free survival, distant disease-free interval, and overall survival. Similarly, the incidence of adverse events was slightly higher among patients in the PBI group, but not statistically significant.

In a discussion about the study following the presentation, Wendy A. Woodward, MD, of MD Anderson Cancer Center in Houston, TX, noted that in general, changes in radiotherapy delivery and technology have made it significantly less toxic, allowing it to become an increasingly realistic and attractive option for women with breast cancer. However, further research on accelerated partial breast irradiation (APBI) modalities such as the one used in this trial should include consideration of alternative schedules and techniques to improve therapeutic as well as cosmetic outcomes. "Updates of consensus guidelines for APBI and further integration of these results with published randomized trials using alternate techniques and regimens without significant toxicity are warranted," she concluded.

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