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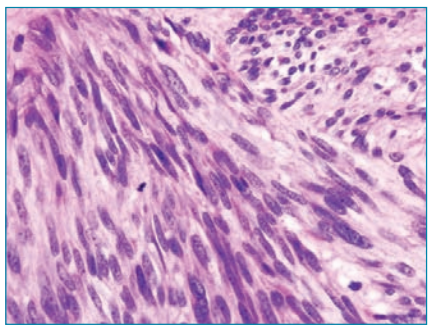

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PERIODICALS

Exemestane Offers New Option to Prevent Breast Cancer in Postmenopausal Women

BY MARK FUERST

CHICAGO — The aromatase inhibitor exemestane can now be considered a new option for breast cancer prevention in postmenopausal women. The results of a large, randomized, double-blind Phase III trial reported at the ASCO Annual Meeting here show that the use of exemestane leads to a 65% reduction in the risk of breast cancer compared with placebo among postmenopausal women who are at increased risk of developing breast cancer.

"Because of the significant reduction of breast cancer and excellent safety profile of exemestane, it has the potential for wider-scale implementation than the selective estrogen receptor modulators [SERMs]," said principal investigator Paul E. Goss, MD, PhD, Professor of Medicine at Harvard Medical School and Director of Breast Cancer Research at Massachusetts General Hospital Cancer Center.

The Discussant for the study, Andrea DeCensi, MD, of E.O. Ospedali Galliera in Genoa, Italy, called the report "a landmark study that would likely result in a paradigm shift in breast cancer prevention. Avoiding breast cancer with manageable toxicity is possible today."

The same day of the ASCO presentation (*Abstract LBA504)*, the study results were also published in the June 4 online version of the *New England Journal of Medicine* and it was subsequently published in the June 23 issue (*NEJM 2011;364:2381-2391*).

SERMs such as tamoxifen and raloxifene reduce breast cancer risk by about 38% and are approved in the United States for breast cancer prevention, Dr. Goss said. "But rare serious side effects, such as endometrial cancers, blood clots, and strokes, have in part limited the use of tamoxifen to about 4% of women at increased risk."

Aromatase inhibitors are superior to tamoxifen in early breast cancer, reducing the occurrence of new cancers in the opposite breast, which is a prevention benefit. Exemestane is one of the three aromatase inhibitors approved for breast cancer treatment, including anastrozole and letrozole. "Exemestane causes less bone loss and thus was our first choice for a breast cancer prevention trial," he said.

The MAP.3 (Mammary Prevention Trial-3) study, led and coordinated by Canada's NCIC Clinical Trials Group, is the first randomized trial to assess an aromatase inhibitor as a breast cancer preventative in healthy women. The trial enrolled 4,560 women, median age of 62,from the US, Canada, Spain, and

continued on page 23

→PERSONALIZED

continued from page 21

Meanwhile patients on unmatched Phase I trials had a median time to treatment failure of 2.2 months on their Phase I regimen and 2.8 months on their prior regimen, which were not statistically different.

"This finding, with an intra-patient comparison, further supports the effectiveness of the matched therapy and the superiority of the personalized medicine approach compared with the standard approach," Dr. Tsimberidou concluded.

"This is hugely better than we've done historically in Phase I trials and I think it is a genuinely cool approach."
—George W. Sledge, Jr., MD

Discussant: Commendable, but Not Randomized, Study

During her discussion of the abstract, Paula M. Fracasso, MD, PhD, the Lawrence W. Penniston, MD, Family Professor of Women's Oncology Research and Deputy Director of the Cancer Center at the University of Virginia School of Medicine, agreed that the approach was important, but she too emphasized that it was not a randomized trial. "I don't think we can make comparisons between groups," she said.

That caution aside, she said, the study was commendable. "At this point our treatment guidelines are organ specific. We absolutely have to change the paradigm." "The MD Anderson Cancer Center initiative is amazing, really. It is an enormous tome of work. It is the first incredible attempt at personalized treatment of cancer—and I take my hat off to them."

Expanding the Approach

Both Dr. Tsimberidou and senior author Razelle Kurzrock, MD, Professor and Chair of the Department of Investigational Cancer Therapeutics at MD Anderson, say this is only the beginning of the effort.

RAZELLE KURZROCK, MD, "This is a big shift for Phase I trials, a big shift for oncology, but sometimes simple concepts make a difference."

In the short term, the researchers plan to continue testing patients' tumors before enrolling them in Phase I trials and matching them where they can. They hope that with better molecular tests, including multiplex assays and more known mutations, they will be able to identify genetic changes in an increasing proportion of patients.

"This is a big shift for Phase I trials, a big shift for oncology," Dr. Kurzrock said. "But sometimes simple concepts make a difference."

For the patients who have multiple mutations, the team has already started working on combination drug trials. "The truth is that we're treating advanced patients," Dr. Kurzrock said. "They are likely to have multiple mutations, so we are working on combination therapies.

"In the first rendition of the study, most of the time we were able to target a single mutation. We now have specific combinations of agents that target some of the most common dual mutations. Of course there could be combinations with more than two drugs, three, or four."

The group's longer-term goal, in collaboration with the Institute for Personalized Cancer Therapy at MD Anderson, is to develop the capability over the next five years to genotype *all* patients treated at the center, which is approximately 30,000 new patients per year. Moreover, as technology improves and more cancer-causing genetic aberrations are found, the team expects to probe hundreds of changes at a time instead of just a few.

The team also aims to test the approach in rigorous clinical trials, so that they can demonstrate conclusively that the personalized matched approach for trials and treatment leads to better response. They aim to make it the new standard of care, and ensure that the costs of the tests will be reimbursed by payers.

"In its simplest form it is just a diagnostic," Dr. Kurzrock said. "We wouldn't think of treating a patient without knowing whether they had colon or lung or breast cancer. And I think it is probably time now that we perhaps shouldn't think about treating a patient unless we know what molecular aberrations they have. The technology is not perfect, but I think we should be using the technology that we have."

→EXEMESTANE

continued from page 22

France who were at least 37 years old and had at least one additional breast cancer risk factor.

Pre-specified risk factors included age 60 or older, a Gail risk score higher than 1.66%, or prior intraepithelial neoplasia (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, or ductal carcinoma in situ with mastectomy). Overall, 49% of the patients were older than 60, 40% had a Gail score higher than 1.66%, and 11% had a prior intraepithelial neoplasia. The women were stratified by Gail score and aspirin use, although the initial evaluation of celecoxib was halted after only a few patients had enrolled.

Participants were randomly assigned to exemestane administered at 25 mg/day for five years (2,285 women) or placebo (2,275 women). After a median follow up of three years, the group receiving exemestane had a 65% reduction in invasive cancers (11 invasive breast cancers in the exemestane group compared with 32 in the placebo group).

The benefit of exemestane, Dr. Goss said, was in the reduction of estrogen receptor (ER)-positive cancers (7 events in the exemestane arm and 27 events in the placebo arm) and in HER2/*neu*-negative cancers (10 and 26 events, respectively).

There was also a 60% reduction of invasive breast cancer plus pre-invasive DCIS among the 66 cases in the women on the trial. Importantly, there were fewer cases of cancer precursor lesions, such as atypical ductal and atypical lobular hyperplasia in the group receiving exemestane, he said.

Exemestane was associated with an increase in the incidence of several adverse events, including hot flashes, fatigue, insomnia, gastrointestinal side effects, and arthritis. However, Dr. Goss noted that the absolute differences were small except for hot flashes, which occurred in 40% of individuals receiving exemestane and 32% receiving placebo.

There were no differences in the incidence of clinical bone fractures, self-reported osteoporosis, cardiovascular events, or other malignancies between arms. The researchers found only minimal differences in health- and menopause-related quality-of-life parameters between the two groups.

"It is improbable that more adverse events will occur after three years," Dr. Goss said at an ASCO news briefing on Women's Cancers. "I am fairly confident that the duration of response and toxicity rate will be good." He added that the efficacy of exemestane is considerably higher than that seen in tamoxifen trials. The best duration of treatment may be between three and five years, he said.

"After unblinding, women on active therapy will be offered exemestane to complete five years, and MAP.3 sites will have the option of offering five years of exemestane to those initially allocated to placebo," he said. "We and others are conducting placebo-controlled trials in healthy women and early breast cancer patients of aromatase inhibitors in menopausal women of similar age, and results from these ongoing trials will contribute to our understanding of long-term efficacies and toxicities of AIs."

ASCO 2011/Scott Morgan

PAUL GOSS, MD: "Because of the significant reduction of breast cancer and excellent safety profile of exemestane, it has the potential for wider-scale implementation than SERMs....Women meeting the criteria of MAP.3, including all women over age 60, and their doctors should be made aware of these results. The potential public health impact of these findings is important."

He noted that long-term results in women with early breast cancer show durable long-term reductions in new breast cancers with exemestane without accumulation of late toxicities.

"Women meeting the criteria of MAP.3, including all women over age 60, and their doctors should be made aware of these results," Dr. Goss said. "The potential public health impact of these findings is important.

"The reduction in breast cancers of 65% we demonstrated was exactly in line with our expectations. The numbers of tumors are small but there also appeared to be fewer of the more aggressive tumors on exemestane. Our study not only showed an impressive reduction in breast cancers, but also an excellent side effect profile. He noted that average follow-up was short – only three years.

Discussant: Study Has Clear Strengths

Dr. DeCensi said the study has clear strengths: "Nearly three-quarters of the breast cancers are ER-positive and account for most deaths. There was a strong rationale based on contralateral breast cancer in other studies."

There was no excess of ER-negative disease among exemestane-treated women, which had been a concern with the approach, he said. He also noted that exemestane was associated with an 85% reduction in the incidence of node-positive cancer, with an annual incidence rate of 0.05% compared with 0.15% with placebo.

"The data show a predictable high activity and excellent safety and tolerability profile," he said.

Study Weaknesses

The study does have weaknesses, he said: "There was a loose definition of high risk and a lack of comparator active arm—for example, raloxifene. So the study can not determine the best hormonal strategy of no estrogen at all versus best balance with a SERM. One major weakness is the lack of follow-up DEXA for osteoporosis detection. This was only self-reported so there is a risk of under-reporting of osteoporosis."

Another concern is that the study was powered for only 38 invasive cancers for a final analysis of three years and 1.2 years of follow-up. "This is too short a follow-up for prevention intervention," he said. "The clinical significance remains to be established."

Being provocative, Dr. DeCensi said, "this could be considered a very large Phase II study that shows clear activity of exemestane, but it remains a proof of principle that long-term safety and risk assessment needs to be established.

"The main purpose of cancer prevention is avoiding the trauma of cancer diagnosis, which is a very meaningful task to real people." There is limited use of SERMs for breast cancer prevention in the United States, he said, and there is no license for this indication outside the US and Canada.

Exemestane is an effective, non-toxic agent, he said, and treating at-risk people and emphasizing the importance of using biomarkers has a huge impact on overall mortality. "The MAP.3 study is a new standard of care for at-risk postmenopausal women. We have to be aware in oncology that any drug that affects cell growth can not be totally devoid of adverse events. It is very important that the medical oncology community spread the notion that most breast cancers are preventable. In the use of exemestane in clinical practice, we have to look for approval of this drug in this indication."

Choices

In an interview, Andrew Seidman, MD, Attending Physician in the Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center, said that the data offer another potential opportunity for women to prevent breast cancer. Prophylactic surgery is another means of reducing the risk of breast cancer. This is a dialogue patients need to have with their doctors, whether to choose surgery or drug therapy."

For women who are at high risk of breast cancer who are obese, sedentary, have coagulopathy disorders, and have a prior history of phlebotomy, an aromatase inhibitor is the preferred option. For women with osteoporosis, a SERM, which has a predictable efficacy on bones, may be a better choice, he said.

"We now have three effective systemic therapies – tamoxifen, raloxifene, and exemestane – that can reduce the risk of a woman having breast cancer," said Dr. Seidman. "Each of these has different side effect profiles. A woman should discuss the most appropriate intervention for her based on her individual medical condition."

"The MAP.3 study is a new standard of care for at-risk postmenopausal women. We have to be aware in oncology that any drug that affects cell growth cannot be totally devoid of adverse events. It is very important that the medical oncology community spread the notion that most breast cancers are preventable."