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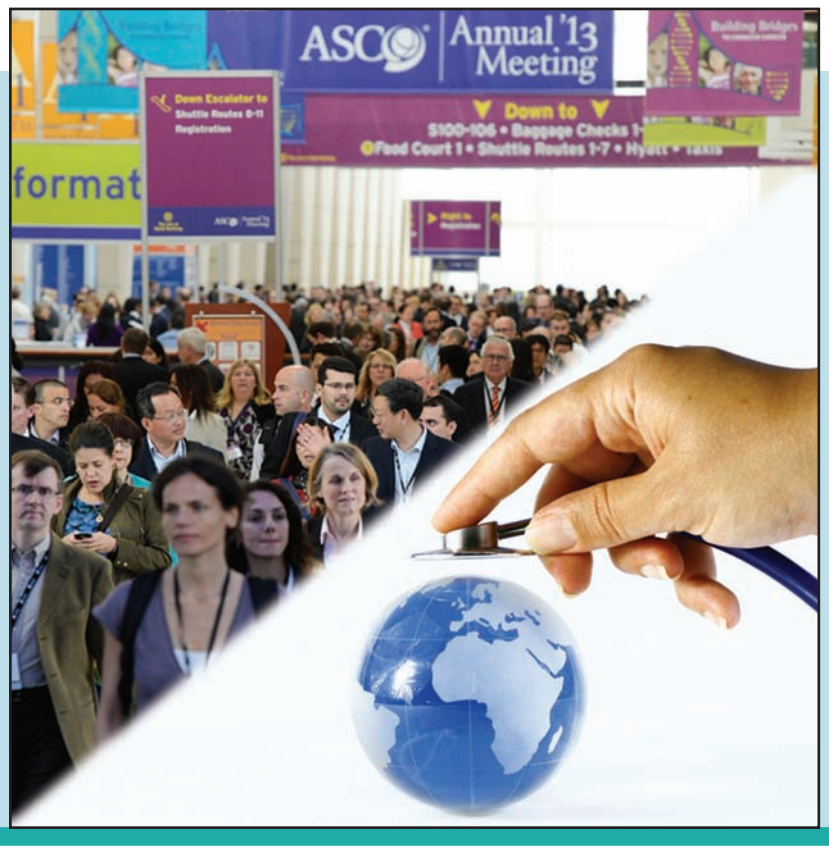

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ASCO and others on how to improve health equity for all

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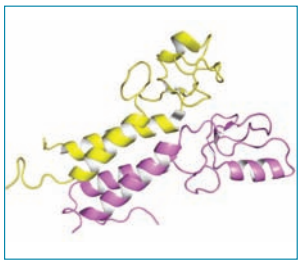

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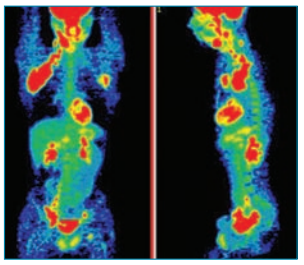

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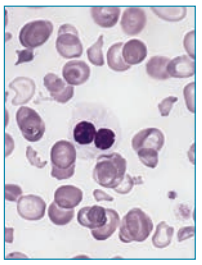

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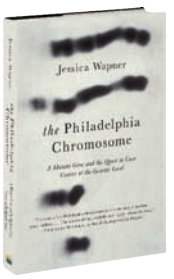

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New ASCO Breast Cancer Risk-Reduction Guideline Urges Discussing Chemopreventive Drugs

BY PEGGY EASTMAN

The American Society of Clinical Oncology has updated its clinical practice guideline for breast cancer prevention in high-risk women, issuing a strong recommendation for oncologists to discuss the use of tamoxifen, raloxifene, and exemestane with eligible high-risk women.

Today, such discussions on chemoprevention and breast cancer risk reduction occur infrequently, the Society notes. As a result, although it has been estimated that more than two million U.S. women could benefit from chemoprevention agents, data from a National Health Interview Survey cited show that there has been no overall increase in the use of tamoxifen and raloxifene in this group despite the fact that the drugs' benefits in high-risk women have been known for up to a decade.

The updated guideline comes at a time when many cancer-related organizations, including the American Cancer Society, are urging a greater emphasis on cancer-prevention strategies; breast cancer is the most frequently diagnosed cancer worldwide.

The guideline, available online ahead of print in the *Journal of Clinical Oncology* (***doi: 10.1200/JCO.2013.49.3122***), updates the original guideline, published in 1999, and subsequent updates published in 2002 and 2009. As with all ASCO guidelines, the document notes that it is "not intended to substitute for the independent professional judgment of the treating physician."

A key message is the strong, evidence-based recommendation that tamoxifen and raloxifene "should be discussed as an option" with eligible high-risk women to prevent breast cancer. The 2009 guideline used the phrase "may be offered" for these drugs, a much weaker recommendation.

This update includes a strong recommendation for oncologists to discuss the use of tamoxifen, raloxifene, and exemestane with eligible high-risk women. (The most recent earlier version, in 2009, had instead said the drugs "may be offered," a much weaker recommendation.)

Removes Recommendation for Baseline Gynecologic Exam

The new guideline removes the recommendation stating that a baseline gynecologic examination before the start of treatment and yearly examinations thereafter are necessary for women taking tamoxifen, reasoning that there is little evidence that such annual examinations led to an earlier detection of uterine cancer.

This version also updates the advice for exemestane; in 2009, the ASCO guideline stated that the use of aromatase inhibitors "is not recommended outside of the clinical trial setting to lower BC [breast cancer] risk." The new evidence-based guideline states that exemestane "should be discussed as an alternative to tamoxifen and/or raloxifene" for risk reduction in selected postmenopausal women. The evidence base for this advice is considered "moderate."

While exemestane is approved for the treatment of breast cancer, the U.S. Food and Drug Administration has not yet approved its use in breast cancer prevention. The ASCO guideline recommendation is based on encouraging data from a single clinical trial that showed up to a 70 percent reduction in overall and ER-positive invasive breast cancer incidence with exemestane compared with placebo over a three-year period.

While the chemoprevention drugs discussed in the new guideline have risks and are not for every woman, carefully selected patients should have the option of taking the drugs because in these women the therapies "can reduce the risk of breast cancer by up to 50 percent," said lead author Kala Visvanathan, MBBS, MHS, Co-chair of the ASCO Guideline Panel and Associate Professor of Epidemiology and Oncology at Johns Hopkins Bloomberg School of Public Health and the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.

She said that today there is a better understanding of which patients will derive benefit from these drugs, benefits that outweigh the risks of taking them.

Asked why the three drugs discussed in the guideline are not more widely used for breast cancer prevention in high-risk women, given their effectiveness, she said via e-mail that this is due to "a number of factors, including the need to have their breast cancer risk assessed first— this is not always done— and concerns about side effects given that they are cancer free."

Increase Use?

Asked if she expects that the guideline will increase use of chemoprevention agents for breast cancer risk reduction, she said, "My hope is that these guidelines highlight the potential benefit of chemoprevention for breast cancer in women at increased risk over the long term and highlight the fact that there are certain groups of women where the benefit does outweigh the risks.

"I see prevention as an important part of cancer care, particularly with an aging population."

Contraindications

The updated guideline specifies that tamoxifen and raloxifene are not recommended for use in women with a history of deep vein thrombosis, pulmonary embolus, stroke, transient ischemic attack, or during prolonged immobilization. Additionally, tamoxifen should not be used in women who are pregnant or may become pregnant, in nursing mothers, or in combination with hormone therapy.

In some cases the risk/benefit clinical decision on treatment is complex—for example, while older women are at higher risk of breast cancer, they are also more likely to have a stroke or develop a blood clot.

The document notes that the new guideline is based on a systematic review of the professional literature; six chemoprevention agents were identified: tamoxifen, raloxifene, arzoxifene, lasofoxifene, exemestane, and anastrozole.

The Co-Chair of the ASCO Guideline Panel, Scott M. Lippman, MD, a longtime chemoprevention researcher who is now Director of the University of California San Diego (UCSD) Moores Cancer Center, noted that when the preventive therapies discussed were developed, they "marked a historic advance in reducing the risk of breast cancer."

Lippman, also Senior Associate Dean and Associate Vice Chancellor for Cancer Research and Care and Professor of Medicine at UCSD School of Medicine, said in a statement that when the risk-reduction drugs are used with ASCO's decision aid tool (*accessible at **asco.org/guidelines/bcrr***), their use in clinical practice can be refined "so that they can provide ever-greater benefit to women at higher risk of breast cancer."

The *JCO* guideline article notes that risk of breast cancer may be determined

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Key Recommendations in the New ASCO Guidelines

1. **Tamoxifen** (20 mg per day orally for five years) should be discussed as an option to reduce the risk of invasive estrogen receptor (ER)-positive breast cancer in premenopausal or postmenopausal women.

2. **Raloxifene** (60 mg orally per day orally for five years) should also be discussed as an option to reduce the risk of invasive, ER-positive breast cancer in postmenopausal women.

3. **Exemestane** (25 mg per day orally for five years) should be discussed as an alternative to reduce the risk of invasive, ER-positive breast cancer in postmenopausal women.

4. All three chemopreventive agents should be discussed (including risks and benefits) with women age 35 years or older without a personal history of breast cancer who are at increased risk of developing invasive breast cancer, based on risk factors such as the woman's age, race and medical and reproductive history.

FDA Approves Gilotrif for Type of Late-Stage NSCLC with Companion Diagnostic

The U.S. Food and Drug Administration has approved the use of Gilotrif (afatinib) to treat patients with metastatic non-small cell lung cancer whose tumors express specific types of epidermal growth factor receptor gene mutations. The drug is a tyrosine kinase inhibitor that blocks proteins that promote cancer cell growth, and is intended for patients whose tumors express the EGFR exon 19 deletions or exon 21 L858R substitution gene mutations.

Also approved was the therascreen EGFR RGQ PCR Kit, a companion diagnostic that helps determine if a patient's lung cancer cells express the EGFR gene mutations.

"The approvals further illustrate how a greater understanding of the underlying molecular pathways of a disease can lead to the development of targeted treatments," Richard Pazdur, MD, Director of the FDA's Office of Hematology and Oncology Products, said in a news release. "Gilotrif is the second drug approved this year for patients with untreated metastatic NSCLC whose tumors have the EGFR exon 19 deletions or exon 21 L858R substitution mutations."

The FDA approved Tarceva (erlotinib), concurrently with the companion diagnostic cobas EGFR Mutation Test, for first-line treatment of patients with NSCLC in May (***OT, 6/10/13 issue***). Gilotrif was approved under the FDA's priority review program, which provides an expedited review for drugs that may provide safe and effective therapy when no satisfactory alternative therapy exists, or offer significant improvement compared with marketed products.

Gilotrif's approval is based on a clinical study of 345 patients with metastatic NSCLC with EGFR mutations, randomly assigned to receive the drug or up to six cycles of pemetrexed and cisplatin. Progression-free survival was 4.2 months longer in patients receiving Gilotrif compared with those receiving the chemotherapy drugs. There was no statistically significant difference in overall survival.

The approval of the therascreen EGFR RGQ PCR Kit was based on data from the clinical study used to support Gilotrif's approval.

Common side effects of the drug include diarrhea, acne-like skin breakouts, dry skin, pruritus, inflammation of the mouth, paronychia, decreased appetite, weight loss, cystitis, nose bleed, runny nose, fever, eye inflammation, and hypokalemia. Serious side effects include diarrhea that can result in kidney failure and severe dehydration, severe rash, lung inflammation, and liver toxicity.

Gilotrif is marketed by Boehringer Ingelheim Pharmaceuticals, Inc., and the therascreen EGFR RGQ PCR Kit is manufactured by QIAGEN Manchester Ltd.

→BREAST CANCER RISK REDUCTION

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by the Gail model, the National Cancer Institute Breast Cancer Risk Assessment Tool (a modified version of the Gail Model), and other validated risk models.

Women are deemed to be at increased risk if their projected absolute risk of developing breast cancer in the next five years is greater than or equal to 1.66 percent.

BRCA1/2 Mutation Carriers

Mutation carriers would seem likely to be among those receiving the most benefit from the new recommendations, but the new guideline states that there are "insufficient data" on the efficacy of tamoxifen for breast cancer risk reduction in BRCA1 and BRCA2 mutation carriers to give reliable estimates of its effect in this prevention setting. Phase III trial data are lacking on the preventive effect of raloxifene and aromatase inhibitors specifically in women with these mutations, the panel found.

A recent symposium for the American Cancer Society related to its 100th year anniversary (***OT, 6/25/13 issue***) highlighted the increasing US rate of obesity, a risk factor for some cancers. Fortunately for obese women at increased risk of breast cancer, the new ASCO guideline states that there is "no direct evidence to suggest that women who are overweight or obese should not be offered tamoxifen or raloxifene for breast cancer prevention."

In an analysis of data from two major trials, "there was no significant interaction found between BMI, treatment group, and incidence of invasive breast cancer," the guideline states.

Talking Points

In order to arrive at the best treatment decision and achieve the best compliance, women need good communication with health professionals, the ASCO guideline emphasizes, noting that discussions with high-risk patients about risk-reducing drugs should include the following points:

> The guideline comes at a time when many cancer-related organizations, including the ACS, are urging a greater emphasis on cancer-prevention strategies.

- Assessment and discussion of the individual risk of developing breast cancer;
- Options for reducing the risk of developing breast cancer (non-pharmacologic as well as pharmacologic);
- Potential impact of specific chemoprevention agents on the incidence of both invasive and noninvasive breast cancers;
- Potential risks and adverse effects of chemoprevention agents;
- Long-term effectiveness of chemoprevention agents;
- The fact that chemoprevention studies were not powered to detect differences in mortality, because it was considered that a reduction in incidence was itself an important clinical endpoint;
- Accessibility, cost, and insurance coverage;
- Patient resources and materials for consideration; and
- A plan for follow-up.