Breast Cancer Prevention in High-Risk Women: Searching for New Options

By Nancy J. Nelson

PARP [poly (ADP-ribose) polymerase] inhibitors, which are getting a lot of attention in the cancer treatment world, will soon make their debut in prevention studies. This summer, two small phase II trials will start enrolling women in the highest-risk group—BRCA1/2 mutation carriers—who will take the PARP inhibitor ABT-888, or veliparib. Investigators will then analyze biomarkers to see whether taking the drug is associated with reduced risk.

After that, the women will undergo mastectomy, a prevention option they will have chosen before enrolling in the trial and one that highlights the dilemma that high-risk women outside of trials face.

“There are few good prevention agents for normal individuals with BRCA mutations,” said Brian Leyland-Jones, M.D., Ph.D., at Emory University in Atlanta, who is leading one of the trials.

Surgery Often the Choice

Regulatory agencies in Europe and the U.S. have approved two hormonal agents, tamoxifen and raloxifene, for reducing breast cancer risk; lasofoxifene, another selective estrogen receptor modulator (SERM), has been approved in Europe but not the U.S. But the SERM trials have not included many BRCA carriers, which makes drawing any conclusions about the effect of the SERMs on this high-risk group hard. Moreover, the SERMs don’t affect the risk of ER-negative tumors and decrease the risk of ER-positive tumors by only about half.

Some oncologists, such as Claudine Isaacs, M.D., at the Lombardi Comprehensive Cancer Center at Georgetown University in Washington, D.C., generally consider chemoprevention only for BRCA2 carriers. “Because BRCA1 carriers tend to develop triple-negative breast cancers, it’s not clear that tamoxifen will work on them,” Isaacs said.

That leaves surgical removal of the breasts or ovaries the frequent choice of women who have tested positive for BRCA1/2 mutations. These women have a 56%–84% chance of developing breast cancer in their lifetime, and prophylactic mastectomy lowers that risk by 90% in observational studies. A 50% reduction is associated with prophylactic removal of the ovaries when done before age 50 years. An article last year in the Journal of the American Medical Association reported that 73% of BRCA1/2 carriers have prophylactic oophorectomies and 48% choose mastectomies.

Other high-risk women may also consider surgery, including those with a personal history of breast cancer who test negative for BRCA mutations; those who have mutations for PTEN or p53; and those who have had repeated biopsies for atypical hyperplasia or lobular carcinoma in situ (LCIS).

“There are some women who keep developing LCIS or atypical hyperplasia, and have had six to eight biopsies, and at this point choose mastectomy,” said Mary Daly, M.D., Ph.D., who chairs the department of clinical genetics at Fox Chase Cancer Center in Philadelphia.

Daly also said she recommends tamoxifen to higher-risk women with LCIS or atypical hyperplasia. The trials, she noted, showed that these women had a greater benefit than those with a family history of breast cancer alone.

PARP Inhibitor Trials

In the two PARP prevention trials, BRCA1/2 carriers will undergo a breast biopsy, followed by a 12-week course of veliparib, one of the agents now in treatment trials. These inhibitors target the PARP pathway, which is involved in repairing DNA single-strand breaks. The studies will test the women’s tolerance of this PARP inhibitor, as well as its ability to modify measurable biomarkers in the breast tissue or blood.
The Emory trial, sponsored by the Eastern Cooperative Oncology Group, will randomize 111 women to receive one or two doses of veliparib or placebo. The other trial is a single-arm dose escalation study involving about 80 women, funded by the Komen Foundation and led by Judy Garber, M.D., of the Dana–Farber Cancer Institute in Boston. The trials will look for changes in breast tissue biomarkers, such as PAR, PARP1, γ-H2AX, cyclin D1, aldehyde dehydrogenase, and the degree of atypical hyperplasia.

Investigators have used biomarkers to study other prevention agents in phase II trials in high-risk women, according to Barbara K. Dunn, M.D., Ph.D., at the National Cancer Institute. In one study, women with hyperplasia took DFMO (difluoromethylornithine) to see whether certain biomarkers in the breast, such as p53, epidermal growth factor receptor, and serum insulin-like growth factor 1, were altered. No change was seen. Likewise, no changes in biomarkers occurred in trials with perillyl alcohol, celecoxib, and letrozole. Other agents currently undergoing testing are atorvastatin (Lipitor), sulindac, and beoxarotene (Targetin).

**Aromatase Inhibitors and Bisphosphonates**

More promising are the results to date with aromatase inhibitors (AIs) as preventive agents. Like tamoxifen and raloxifene, AIs are estrogen-targeted agents, but rather than acting directly on the estrogen receptor, they block the activity of the enzyme aromatase, which is necessary to make estrogen. The potential of AIs as prevention agents, Dunn said, was recognized when treatment trials for three AIs, anastrozole, exemestane, and letrozole, showed a reduction in cancers in the other breast.

Two current phase III prevention trials are testing AIs. The European study, IBIS-II, is comparing anastrozole to a placebo in postmenopausal women at increased risk of breast cancer as well as women with ductal carcinoma in situ. A Canadian prevention trial, MAP.3, is testing exemestane versus placebo in women at increased risk of breast cancer.

As for other potential prevention agents, Dunn pointed to a few with some tantalizing data. One is a class of compounds known as bisphosphonates, which are approved for treating osteoporosis and skeletal metastases in cancer patients. In a recent treatment trial in premenopausal women published in 2009 in the *New England Journal of Medicine*, a bisphosphonate, zoledronic acid, was added to tamoxifen or anastrozole. The combination resulted in a statistically significant increase in disease-free survival rate from 90.8% to 94.0%. Although the incidence of cancer in the other breast declined, this decrease was not statistically significant.

Even as potential prevention agents emerge, however, clinicians must deal with the fact that they cannot easily identify women at high risk.

“Many women who develop breast cancer are not known to be at high risk,” pointed out Amy C. Degnim, M.D., associate professor of surgery at the Mayo Clinic in Rochester, Minn. “We are still unable to reliably predict breast risk for most women.”

© Oxford University Press 2011. DOI: 10.1093/jnci/djr159