Targeted Therapy Looks Promising for High-Risk Breast Cancer

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A new type of breast cancer treatment led to longer survival, fewer serious side effects and better quality of life for women who carry BRCA mutations, which raise the risk of breast cancer and other malignancies, according to a study presented at the American Society of Clinical Oncology (ASCO) annual meeting this week in Chicago.

Lynparza (olaparib) was nearly twice as likely as chemotherapy to shrink tumors in women with metastatic breast cancer, and it extended survival by three months, Mark Robson, MD, of Memorial Sloan Kettering Cancer Center in New York City reported.

“It is especially encouraging to see that [Lynparza] was effective against triple-negative breast cancers that arise in women with inherited, germline BRCA mutations,” Robson said. “This type of breast cancer is particularly difficult to treat and often affects younger women.”

Targeted therapy that works against cancer with specific genetic mutations is becoming a mainstay of treatment. This type of therapy is often better tolerated than traditional chemotherapy, which kills not only cancer cells but also rapidly dividing healthy cells throughout the body.

Lynparza works by blocking poly (ADP-ribose) polymerase, or PARP proteins, which play a role in DNA damage response. PARP inhibition results in more DNA breaks that can halt cell division. Lynparza and another PARP inhibitor, Rubraca (rucaparib), are currently approved for advanced ovarian cancer in women who test positive for BRCA mutations.

Women with inherited BRCA1 or BRCA2 gene mutations are at higher risk for breast and ovarian cancers. Around half of women who carry these mutations will develop breast cancer, according to the National Cancer Institute. Black women are less likely than white women to have the BRCA1 mutation but more likely to have the BRCA2 mutation. (These are known as “germline” mutations, as opposed to “somatic” mutations, which arise later in life.)

People with these BRCA mutations do not make proteins that repair DNA and suppress tumors. These proteins are needed to fix DNA damage caused by PARP inhibition, so BRCA-related cancers are especially vulnerable to drugs that block PARP—a phenomenon known as “synthetic lethality.”

Robson presented findings from the international Phase III OlympiAD study, which enrolled 302 participants with hormone receptor-positive or triple-negative breast cancer. Triple-negative tumors do not express hormone receptors or another receptor called HER2, so therapies targeting these receptors don’t work.

All but seven participants were women, and the median age was 44 years. More than 50 percent had the BRCA1 mutation, more than 40 percent had BRCA2 and a small number had both. Half had hormone receptor-positive and half had triple-negative breast cancer. They had metastatic cancer (spread beyond the breast), and most had previously used various kinds of hormone therapy and chemotherapy.

Participants were randomly assigned to receive 300 milligram Lynparza tablets twice daily or chemotherapy using Xeloda (capecitabine), Halaven (eribulin) or Navelbine (). Xeloda is a pill, but the other drugs require IV infusion. Participants were treated until they experienced disease progression.

The overall response rate—meaning complete or partial tumor shrinkage—was 60 percent in the Lynparza group, compared with 29 percent in the chemotherapy group. Nine percent and 2 percent, respectively, experienced complete response, or tumor disappearance. The median duration of response in the two groups was 6.2 and 7.1 months.

The median duration of progression-free survival—meaning that patients were still alive with no worsening of disease—was 7.0 months in the Lynparza group, compared with 4.2 months in the chemotherapy group, representing a 42 percent improvement. However, overall survival ended up being about the same, as cancer cells developed resistance to the drug (19.3 months and 19.6

months, respectively).

About three quarters of study participants eventually stopped treatment due to disease progression. Severe side effects were seen less often in the Lynparza group (37 percent) than in the chemotherapy group (51 percent). Five percent and 8 percent, respectively, discontinued treatment for this reason. Nausea, vomiting and anemia occurred more often on Lynparza, while neutropenia (low white blood cell count) was more frequent on chemotherapy.

Among patients with pre- and post-treatment assessments using a 100-point standardized scale, average quality of life rose by four points in the Lynparza group, while falling by about the same amount in the chemotherapy . The improvement was small but considered clinically meaningful, according to Robson.

“Olaparib will probably be best used early in the course of metastatic breast cancer,” Robson said. “It helps preserve patient quality of life, offers the chance to postpone the need for IV chemotherapy and avoids side effects like hair loss and low white blood cell counts.”

Commenting on the study during an ASCO plenary session devoted to studies deemed to have the greatest potential impact on patient care, Allison Kurian, MD, of Stanford School of Medicine, predicted that these results would be “practice-changing.” She also said we need to think about Lynparza and similar PARP inhibitors for other BRCA-related cancers.

Complete results from the OlympiAD study were published in the June 4 advance edition of The New England Journal of Medicine and are available for free online.

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