エキセメスタンは健常女性の乳がんリスクを軽減させる（Abstract No.LBA504）

アロマターゼ阻害薬は高リスクの閉経後女性における浸潤性乳がんリスクを軽減する

Aromatase inhibitor significantly reduces risk of invasive breast cancer in high-risk, postmenopausal women

2011年ASCOで発表されNew England Journal of Medicineオンライン版に掲載された大規模無作為化二重盲検Phase IIIトライアルの結果、乳がん発症リスクの高い閉経後女性においてアロマターゼ阻害薬エキセメスタンが乳がん発症リスクを65%低下させることが示された。MAP.3（乳がん予防トライアル：Mammary Prevention Trial-.3）スタディは健常女性におけるアロマターゼ阻害薬の乳がん予防効果を評価した初めての無作為化トライアルである。このトライアルは、リスクファクター（60歳以上；5年Gailリスクスコア1.66%超；異型乳管または小葉過形成または上皮内小葉がんの既往；または乳房切除術後の上皮内乳管がん）を1つ以上有する閉経後女性4,560人を組み入れた。フォローアップ期間中央値3年後に、浸潤性がんはエキセメスタン群において65%少なかった（浸潤性乳がんはエキセメスタン群で11人に対しプラセボ群で32人）。このトライアルの患者66症例において浸潤性乳がんと前浸潤性DCISが60%減少した。重要なことに、異型乳管または異型小葉過形成などの前駆病変もエキセメスタン群において少なかった。

Full Text

A large randomized double-blind phase III trial led by Canada's NCIC Clinical Trials Group (NCIC CTG) has shown that in postmenopausal women who are at increased risk of developing breast cancer, the aromatase inhibitor (AI) exemestane (Aromasin) reduces this risk by 65 percent compared with placebo.

"The potential public health impact of these findings is important. Worldwide it is estimated that 1.3 million women are diagnosed with breast cancer each year and nearly 500,000 women die of the disease. Results from the MAP.3 trial indicate that exemestane is a promising new way to prevent breast cancer in menopausal women most commonly affected with breast cancer," said Paul E. Goss, M.D., Ph.D., lead study author and professor of medicine at Harvard Medical School and Massachusetts General Hospital in Boston, MA.

"The reduction in breast cancers of 65 percent we demonstrated was exactly in line with our expectations," Dr. Goss continued. "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, although my cautionary note is that average follow-up to date has been only 3 years."

Estrogens have been implicated in causing breast cancer. The anti-estrogens tamoxifen and raloxifene are FDA approved preventatives of breast cancer in women at high risk. However, it has been estimated that rare but serious uterine cancer and blood clots which can be fatal, have limited the acceptance of tamoxifen to only 4 percent of high risk women and 0.08 percent of all women in the U.S. There is a need for highly effective and safer options for breast cancer prevention.

Aromatase inhibitors (AIs) powerfully prevent estrogen synthesis and are distinct from tamoxifen in the way they counteract estrogen. AIs are superior to tamoxifen in preventing recurrences in early breast cancer patients, including the prevention of new breast cancers. The investigators predicted from laboratory experiments and clinical results that AIs would prevent breast cancer without the serious toxicities seen with tamoxifen.

The MAP.3 (Mammary Prevention Trial-.3) study, led and coordinated by the NCIC CTG, is the first randomized trial to assess an aromatase inhibitor as a breast cancer preventative in healthy women. Exemestane is an AI approved by the U.S. Food and Drug Administration for use in early breast cancer patients. The trial enrolled 4,560 women from the U.S., Canada, Spain and France.

Eligible postmenopausal women had at least one of these risk factors: age greater than or equal to 60 years; five-year Gail risk score greater than 1.66 percent; prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ; or ductal carcinoma in situ with prior mastectomy.

At a median follow up of three years, the group receiving exemestane had a 65 percent reduction in invasive cancers (11 invasive breast cancers in the exemestane group compared to 32 in the placebo group). There was also a 60 percent 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.

The investigators reported symptoms such as hot flashes, fatigue sweating, insomnia and arthralgia were frequent in all women on study but predictably slightly more common on exemestane. However, these symptoms did not appear to affect self-reports of overall health-related quality of life on exemestane.

More serious adverse events including bone fractures, osteoporosis, hypercholesterolemia, adverse cardiovascular events and other non-breast cancers were equal in both groups.

"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. We and others are conducting placebo-controlled trials in healthy women and early breast cancer patients of AIs in menopausal women of similar age and results from these ongoing trials will contribute to our understanding of long term efficacies and toxicities of aromatase inhibitors," Dr. Goss said. "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. So we are hopeful and optimistic that this will be the case in this prevention setting."

The study was supported by the Canadian Cancer Society; Pfizer Inc. PEG supported in part by Avon Foundation.

ASCO2011特集