Breast Cancer

Finding: Treatment with the aromatase inhibitor exemestane reduced the development of invasive breast cancer by 65%.

Approach: A randomized, double-blind trial of 4,560 postmenopausal women compared exemestane to placebo over 3 years.

Impact: Significant reduction in breast cancer risk may be achieved with a class of drugs that has fewer side effects than the traditional SERMs.

EXEMESTANE PREVENTS INVASIVE BREAST CANCER IN POSTMENOPAUSAL WOMEN

The current standard for chemoprevention of breast cancer involves selective estrogen-receptor modulators (SERM), including tamoxifen and raloxifene. Tamoxifen has been shown clinically to reduce breast cancer risk significantly, but its use is associated with serious side effects due to antiestrogenic actions on tissues aside from the breast, especially endometrial cancer and venous thromboembolism. Exemestane belongs to the class of drugs called *aromatase inhibitors*, which also antagonize the actions of estrogen but do so by blocking its synthesis in peripheral tissues, such as the breast. In a randomized, double-blind, placebo-controlled trial, Goss and colleagues showed that exemestane reduced the annual incidence of invasive breast cancer by 65%, without any associated serious adverse events and only minimal quality-of-life differences compared to placebo. A total of 4,560 postmenopausal women who were at moderately increased risk for breast cancer—meaning they had at least 1 study-specific risk factor—were treated with either exemestane or placebo over the course of 3 years. Symptoms and adverse effects were similar between the 2 groups, with menopausal symptoms slightly more frequent in those treated with drug. In addition to the relative reduction in invasive breast cancer in the treatment group, exemestane also reduced the risk of known breast cancer precursor lesions and the more aggressive HER2-positive tumors; a previous study showed an exemestane-related reduction in contralateral breast cancer as well. Overall, the results of the study suggest that the risk-benefit profile of exemestane may be superior to the more traditional SERMs in the primary prevention of breast cancer, and follow-up of treated women may continue to confirm the long-term efficacy of aromatase inhibitors. ■

Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 2011 Jun 4. [Epub ahead of print]

Melanoma

Major finding: Imatinib mesylate demonstrates activity in melanoma with aberrations in *KIT* in a phase II study.

Impact: There is clear activity for targeting KIT in malignant melanoma.

Controversy: Further studies are needed to determine which mutations determine sensitivity and to identify patients most likely to benefit.

KIT IS A THERAPEUTIC TARGET IN MALIGNANT MELANOMA

KIT is a receptor tyrosine kinase that plays a critical role in the development of normal melanocytes. Activating mutations in *KIT* are found in certain cancer types, including gastrointestinal stromal tumors; inhibitors of KIT (e.g., imatinib) are of clinical benefit in such tumors. Although the most common form of melanoma harbors mutation in *BRAF*, several other subtypes of melanoma, including those that arise at mucosal, acral, and chronically sun-damaged sites, were recently found to harbor mutations in *KIT*. However, several phase II clinical trials of imatinib in unselected metastatic melanoma patients failed to show a benefit. Given preclinical and sporadic clinical evidence of response to imatinib, Carvajal and colleagues report results of a study in which patients with *KIT* mutations or amplifications were treated with imatinib. Of 25 evaluable patients, 2 achieved durable complete responses and 2 achieved durable partial responses. Importantly, tumors that harbored mutations at recurrent hotspot sites in the *KIT* gene or showed selection for the mutant allele were more likely to respond to imatinib treatment. These data demonstrate that KIT is a therapeutic target in a subset of melanomas harboring mutations in *KIT* rather than *BRAF*. KIT inhibitors may be of clinical value in a selected patient population based on screening for these genetic alterations. ■

Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman RA, Teitcher J, et al. KIT as a therapeutic target in malignant melanoma. JAMA 2011;305:2327–34.

Note: *Research Watch* is written by *Cancer Discovery* Editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.