

Exemestane May Fare Better Than Tamoxifen for Metastatic Breast Cancer in Postmenopausal Women

Aromatase inhibitors may have potential advantages over tamoxifen, according to growing evidence presented from a phase III trial reported in the October 20 issue of *Journal of Clinical Oncology*. The positive results of a phase II study of exemestane (Aromasin, Pfizer) as first-line therapy for metastatic breast cancer in postmenopausal women, conducted by investigators from the European Organization for the Research and Treatment of Breast Cancer Cooperative Group, led to extension of the study as a phase III randomized trial comparing exemestane with tamoxifen in the same setting.

The study, with a primary endpoint of PFS and secondary endpoints of OS and safety, analyzed 371 women who had either metastatic or locally recurrent inoperable breast cancer and more than 1 measurable lesion. The patients were randomized to receive either 25-mg exemestane (n=182) or 20-mg tamoxifen (n=189) daily. ITT analysis found that the majority of women (93%) had estrogen receptor- and/or progesterone receptor-positive disease.

At 6 months, 66.2% of women in the exemestane group and 49.5% of women in the tamoxifen group had no progression. Analysis at 12 months showed better PFS rates in patients receiving exemestane versus tamoxifen (41.7% vs 31.2%). At a median follow-up of 29 months, 319 women (tamoxifen, 161; exemestane, 158) experienced disease progression or had died. Of the women whose disease advanced, progression occurred less in the exemestane group compared to the tamoxifen group (18.1% vs 28.6%). At this same follow-up, the median treatment duration was 6.5 and 11.5 months in the tamoxifen and exemestane groups, respectively. The overall hazard ratio (HR) favored exemestane; 17 months later—at 46 months—however, the HR for PFS was similar in both groups (HR, 0.87). Safety analyses found that both exemestane and tamoxifen were well tolerated. Early PFS and quality of response were significantly better in patients taking exemestane.

Bevacizumab May Increase Risk Of Venous Thromboembolism

The antineoplastic agent bevacizumab (Avastin, Genentech) is associated with an increased risk of venous thromboembolism (VTE) in patients receiving concur-

rent chemotherapy or cytokine treatment, results of a large meta-analysis reported in the November 19 issue of the *Journal of the American Medical Association* showed. To assess this risk, researchers at Stony Brook University led by Dr. Shobha Rani Nalluri, analyzed 15 randomized controlled trials that included 7,956 patients with advanced solid tumors.

There have been concerns regarding the association of VTE with new agents such as bevacizumab, as cancer itself predisposes patients to thromboembolism along with numerous other factors. The goal of Dr. Nalluri and her colleagues was to overcome the limitations of single trials and, by pooling the data from all 15 clinical trials, to differentiate the effect of bevacizumab on VTE risk, independent of these other factors.

The investigators determined that the overall incidence of all grades of VTE and of high-grade VTE was 11.9% and 6.3%, respectively; the risk of developing VTE was 33% higher with high-dose and low-dose bevacizumab than with controls. In response to these findings, the researchers asserted the importance of recognizing this risk and balancing it against the benefits of bevacizumab.

The highest incidence of VTE was seen in colorectal cancer patients (19.1%), followed by non-small cell lung cancer patients (14.9%), breast cancer patients (7.3%), and renal cancer patients (3.0%). This particularly high incidence in gastrointestinal and pulmonary cancers supports the need for appropriate prophylaxis in patients receiving bevacizumab, researchers said.

Mechanism Behind the Rapid Growth Of Infantile Hemangioma Discovered

A mechanism for the rapid growth of the most common of childhood tumors—infantile hemangioma, which affects up to 10% of children of European descent—has been unveiled, according to a study published in the October 19 issue of *Nature*.

The growth appears within days of birth and presents most frequently as a single, blood-red lump on the head or face; it continues to grow in the following months. The growth of this benign tumor slows as the child gets older and most tumors disappear by the end of puberty. Although these hemangiomas are benign, they can cause serious complications if they obstruct vision, respiration, or other bodily function. Hemangiomas can also cause psychological stress due to the social difficulties of disfigurement.

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The study, conducted by researchers from Harvard Medical School, Harvard School of Dental Medicine, the Children's Hospital Boston, and the de Duve Institute in Brussels, examined tissues isolated from 9 specific hemangioma tumors.

Researchers determined that the endothelial cells lining the affected blood vessels originated from the same abnormal cell; therefore, they concluded that the endothelial cells were the source of tumor growth. The researchers also ascertained that the cells were activated by vascular endothelial growth factor (VEGF) and that at least 2 gene mutations allowed VEGF to prompt unconfirmed growth in the endothelial cells.

Lead researcher Dr. Bjorn R. Olsen from Harvard Medical and Dental schools, saw these findings to open up new treatment options; anti-VEGF therapies are already approved for other types of cancer. Future research will focus on why these tumors grow or regress and how to induce regression in malignant tumors.

Gene Expression Profiling in Hepatocellular Carcinoma May Show Markers Correlated to Survival

A genomewide expression profiling of formalin-fixed, paraffin-embedded tissues revealed that gene-expression signatures that are correlated with survival are present in liver tissue in patients with hepatocellular carcinoma, according to a report in the October 15 issue of *The New England Journal of Medicine*. Researchers, led by Dr. Todd R. Golub, applied this expression-profiling method to tissues from 307 patients with hepatocellular carcinoma.

Currently, it is very difficult to identify patients who, after undergoing treatment for hepatocellular carcinoma, are at the highest risk of recurrence. Genomewide expression profiling requires frozen tissue for analysis; however, collection of such tissues is not routinely performed. On the contrary, most of the specimens that are collected from patients are formalin-fixed. The researchers found that utilizing the expression-profiling method for formalin-fixed tissue was highly effective.

The majority of samples (90%) produced high quality data; some samples were even stored for more than 24 years. Gene-expression profiles of the tumor tissue itself did not correlate with survival; however, it was found that a reproducible gene-expression signature correlated with survival was present in surrounding non-tumoral liver tissue.

This profiling was conducted in a training set of tissues from 82 Japanese patients and validated in tissues from 225 patients from the US and Europe ($P=.04$). The researchers aim to use this test to identify the patients at highest risk for recurrence of hepatocellular carcinoma and to target intensive follow-up or chemopreventive strategies in such patients.

Immunoembolization Safe and Promising For Liver Metastases From Uveal Melanoma

A novel immunoembolization therapy safely achieved regression of unresectable liver metastases from uveal melanoma by utilizing granulocyte-macrophage colony-stimulating factor (GM-CSF), according to a phase I study published in the October 6 issue of *Journal of Clinical Oncology*.

According to researchers, led by Dr. Takami Sato, the benefit of immunoembolization is its ability to attract and stimulate antigen-presenting cells in liver tumors and improve the uptake of tumor antigens released from necrotic tumor cells. Immunoembolization also has the potential to elicit a systemic immune response against tumor cells and thereby stunting the growth of extrahepatic metastases. Uveal melanoma itself can be effectively treated; however, if it metastasizes to the liver, the length of survival can be less than 6 months.

The study enrolled 39 patients (34 with primary uveal melanoma) who received escalating doses of GM-CSF (25 μg starting dose) following hepatic artery embolization at 4-week intervals. Maximum tolerated dose was not reached, even at doses up to 2,000 μg ; side effects at this dose were mild and lasted for 1–2 days (fever, upper abdominal pain, nausea). Of the 34 patients with uveal melanoma, 31 were assessable by radiography; 2 patients had CR, 8 had PR, and 10 had stable disease. Median OS in the intent-to-treat population was 14.4 months and 1- and 2-year survival rates were 62% and 26%, respectively. The mean survival rate in patients who achieved CR or PR was 33.7 months; 1 patient was alive at 40.8 months of follow-up. Longer PFS was seen in patients on higher doses (1,500 μg) of GM-CSF compared to lower doses ($\leq 1,000$ μg).

The study confirmed that immunoembolization with GM-CSF is safe and feasible in patients with hepatic metastasis from primary uveal melanoma. A phase II study comparing embolization with and without GM-CSF is ongoing.