Short-Course Therapy with Xeloda, Taxotere, and Herceptin

**Presenter:** Debu R. Tripathy, MD, Professor of Internal Medicine, University of Texas, San Antonio, Tex.

When investigators at Texas Southwestern Medical Center in San Antonio postulated that the known synergy and good tolerability of three drugs would bring favorable results in patients with early breast cancer, they found that a short course of therapy was beneficial. The combination, which included two chemotherapy agents—capecitabine (Xeloda, Roche) plus docetaxel (Taxotere, Sanofi-Aventis) with the addition of trastuzumab (Herceptin, Genentech)—among women with HER-2–positive (HER-2+) status produced clinical responses in about 75% of those enrolled. (HER is defined as human epidermal growth factor receptor.)

The clinical trial, conducted by Dr. Tripathy, included 156 women (median age, 52 years) with newly diagnosed tumors confined to the breast or to axillary nodes without distant spread; 122 were HER-2–negative (HER-2–), and 34 were HER-2+. They received open-label, oral Xeloda given at a dose of 825 mg/m² twice daily on days 1 to 14 every three weeks and intravenous (IV) Taxotere at a dose of 75 mg/m² on day 1 every three weeks. IV Herceptin was given to the HER-2+ patients at a 4-mg/kg loading dose, then 2 mg/kg on days 1, 8, and 15 every three weeks.

The primary endpoint was the rate of combined pathological complete response (pCR) and near pathological complete response (npCR) of residual tumor up to T1a status in the affected breast after four cycles of Xeloda and Herceptin. The primary endpoint was reached in 15% of HER-2–women and in 50% of HER-2+ women. Although overall clinical response rates were similar for HER-2– patients (76%) and HER-2+ patients (73%), complete responses were nearly doubled in the HER-2+ arm (22% and 42%, respectively).

In the HER-2– and the HER-2+ arms, mean tumor size decreased from 5.6 cm and 6.1 cm at baseline to 1.6 cm and 2.8 cm after four cycles. In the 33 highly treatment-resistant “triple-negative” patients (with HER-2–, estrogen receptor–negative [ER–], and progesterone receptor–negative [PR–] status), the rate of pCR plus the npCR rate was 36.4%. Among women with ER–/PR–/HER-2+ status, the rate was 66.7%.

Dr. Tripathy noted that typical rates for pCR plus npCR after four cycles of chemotherapy ranged from 10% to 15%. Very few patients had to stop therapy because of toxicity.

He concluded: “These results suggest that a short course of Xeloda plus Taxotere is a reasonably active, non–anthracycline-containing preoperative treatment option.”

The findings, he said, justify larger trials comparing combination and standard chemotherapy regimens.

Aromatase Inhibitors and Bone Loss

**Presenter:** Adam Brufsky, MD, PhD, University of Pittsburgh, Pittsburgh, Pa.

The use of aromatase inhibitors can increase disease-free survival in postmenopausal women with estrogen receptor–positive (ER+) or progesterone receptor–positive (PR+) breast cancer, but it also brings about nearly complete ablation of estrogen production, leading to accelerated bone loss and an increased risk of fractures. Although oral bisphosphonates have proven efficacy in postmenopausal osteoporosis, they are often poorly tolerated.

“Compliance can be an issue,” stated Dr. Brufsky.

Dr. Brufsky presented long-term results of the Zometa–Femara Adjuvant Synergy Trial (Z-FAST). This trial evaluated the efficacy and safety of zoledronic acid (Zometa, Novartis) in preventing bone loss associated with aromatase inhibitors in postmenopausal women with early breast cancer who were receiving adjuvant therapy with letrozole (Femara, Novartis). It also compared initial (“up-front”) therapy with treatment that was delayed until either post-baseline T-scores decreased to –2 or below or until a clinical fracture occurred. A T-score of 1.0 is normal, –1.0 represents mild bone thinning, and –2.5 is considered to be osteoporosis.

The trial included 600 postmenopausal women (median age, 60 years) with stage I to III ER+ and/or PR+ breast cancer who were receiving Femara 2.5 mg once daily for five years. The patients were randomly assigned to receive up-front therapy or delayed IV Zometa 4 mg every six months as well as calcium and vitamin D.

The primary endpoint was the percentage of change in lumbar spine bone mineral density. Most women (about 85%) had T-scores between –1 and –2 at the baseline evaluation.

Dr. Brufskey reported changes in bone density after 36 months of treatment in 274 women; 140 women received initial therapy, and 133 received delayed therapy. Lumbar spine bone density increased by a mean of 4% in the patients receiving initial Zometa therapy but dropped by almost 3% in the delayed Zometa group, for a 7% difference (P < 0.001).

Similarly, differences in total bone density of the hip favored...
initial therapy. Among patients with normal baseline T-scores who received up-front Zometa, T-scores dropped to below −2 in 5% of the women. By contrast, in the delayed-therapy group, T-scores dropped to below −2 in 23% to 24% of the women ($P = 0.0024$). In patients with low baseline T-scores (i.e., −1 to −2), T-scores dropped to below −2 in 3% to 4% of patients receiving initial therapy and in 15% to 20% of patients receiving delayed therapy.

Although Z-FAST was not powered to assess fracture rates, Dr. Bruksy said that the overall fracture rates were 5.7% with initial therapy and 6.3% with delayed treatment. He called the finding of a 3.5% rate of disease recurrence in the up-front group, compared with 6.9% in the delayed group, “exploratory” and “somewhat intriguing.”

There were no reports of osteonecrosis of the jaw, a concern in other bisphosphonate trials, and Zometa was generally safe and well tolerated with “no surprises,” Dr. Bruksy said.

He concluded: “Up-front administration of Zometa led to increased lumbar spine and total hip bone mineral density with no differences in fracture rates, as compared with delayed Zometa treatment.”

### Aromatase Inhibitors and Tamoxifen

**Presenter:** James Mansell, MD, Western Infirmary, Glasgow, Scotland

A study that examined the incidence, type, and timing of breast cancer recurrence supports an initial strategy of aromatase inhibitors for women with postmenopausal estrogen receptor–positive (ER+) status, according to Dr. Mansell. He noted that beneficial results from trials of adjuvant aromatase inhibitors have led to the widespread use of these agents, but the continued use of tamoxifen (e.g., Nolvadex, AstraZeneca) as an initial strategy might leave women more vulnerable to recurrence. In major trials, women were switched from tamoxifen to an aromatase inhibitor at a mean of 2.5 years. Distinct recurrences, the prevalent recurrence type in these trials, are known to be a significant predictor of breast cancer–related deaths.

Dr. Mansell evaluated 4,245 ER+ women 50 years of age and older (median age, 62 years) with early-stage breast cancer in the United Kingdom over a median follow-up period of 60 months. At two years, the recurrence rate peaked at 4.2%. Most of these recurrences were at distant sites (3.2%). At 2.5 years, the cumulative recurrence rate was 6.2% (4.5% of recurrences were distant), and at five years, the rate was 13.9%; 9.8% of recurrences were distant, 2.7% were locoregional, and 1.3% were contralateral.

These findings suggest that the distant recurrence is indeed the predominant type in the first two years in postmenopausal women with early stage ER+ breast cancer, said Dr. Mansell, and disease recurs even with treatment with the antiestrogen agent tamoxifen.

He concluded: “We would recommend starting an up-front aromatase inhibitor for all postmenopausal women with ER+ breast cancer, apart from those at particularly low risk of recurrence. There is no reason to wait for 2.5 years.”

### Combined Therapy: Ixempra plus Xeloda

**Presenter:** Hope Rugo, MD, Clinical Professor of Medicine at University of California, San Francisco, Comprehensive Cancer Center, San Francisco, Calif.

Compared with capecitabine (Xeloda, Roche) alone, the combination of ixabepilone (Ixempra, BMS) plus Xeloda nearly doubled progression-free survival among a subset of women with highly treatment-resistant “triple negative” breast cancer, according to Dr. Rugo. Ixempra, a novel semisynthetic analogue of epothilone B, causes cell cycle arrest and apoptosis of actively dividing cancer cells by stabilizing microtubules.

Women who are estrogen and progesterone receptor–negative and HER-2–negative (ER-/PR-/HER-2–) comprise 10% to 20% of those with early breast cancer, but they also comprise a much higher proportion of those with metastatic disease, which is associated with poor response and short survival with standard chemotherapy, Dr. Rugo said.

Dr. Rugo and her colleagues hypothesized that because Ixempra overcomes mechanisms that cause resistance to taxanes and anthracyclines, it might overcome the resistance commonly experienced by these very-poor-risk patients. The open-label study included 752 women (median age, 52.5 years), 25% of whom had triple-negative status (ER–/PR–/HER-2–) with metastatic breast cancer that was resistant to taxanes and that had been pretreated with or was resistant to anthracyclines. The patients were randomly assigned to undergo a 21-day cycle of IV Ixempra at a dose of 40 mg/m² on day 1 plus oral Xeloda at 2,000 mg/m² on days 1 to 14 or to receive Xeloda alone at 2,500 mg/m² on days 1 to 14.

The primary endpoint was progression-free survival. Median progression-free survival was 4.1 months among the 91 women with triple-negative status who were receiving Ixempra/Xeloda and 2.1 months among 96 triple-negative women receiving Xeloda alone.

The overall response rate with these two agents was 27%, compared with 9% for Xeloda alone. In the overall population, progression-free survival was 5.8 months with Ixempra/Xeloda and 4.2 months with Xeloda alone. Response rates were 35% with the combination and 14% with Xeloda monotherapy.

In the combination arm, grade 3 and 4 neutropenia (68%) and sensory neuropathy (21.1%) were manageable with dose adjustments. In the overall population, most grade 3 and 4 peripheral neuropathy was reversible, Dr. Rugo said; in 89% of patients, it resolved to grade 1 or to baseline measures in a median of six weeks. Grade 3 and 4 febrile neutropenia was reported in 5% of patients receiving the combination therapy.

Dr. Rugo commented in an interview: “Our idea is to move this drug much earlier in the treatment of breast cancer to potentially overcome resistance sooner and perhaps treat with curative intent.”

The trial findings, she suggested, confirm the activity of Ixempra in patients with triple-negative status and with anthracycline/taxane-resistant metastatic breast cancer.