Zoledronic Acid (Zometa) plus Neoadjuvant Chemotherapy Have Antitumor Activity

- Matthew C. Winter, MD, Weston Park Hospital, Sheffield, U.K.,
- Presented at a press conference by Robert Coleman, MD, Cancer Research Centre, Weston Park Hospital, Sheffield, U.K.

Zoledronic acid (Zometa, Novartis) is a bisphosphonate indicated for the treatment of hypercalcemia of malignancy in patients with multiple myeloma or in patients with bone metastases from solid tumors. Exploratory evidence from the AZURE trial (Adjuvant Zoledronic acid redUce REcurrence), however, suggests direct antitumor activity when zoledronic acid is added to neoadjuvant chemotherapy in patients with breast cancer. The AZURE investigators recruited 3,360 women with stage II/III breast cancer.

Preclinical studies of nitrogen-containing bisphosphonates showed antitumor activity, and adding zoledronic acid to adjuvant endocrine therapy in premenopausal women with hormone receptor–positive (HR+) breast cancer has significantly prolonged disease-free survival. This new analysis focused on the AZURE subgroup receiving neoadjuvant chemotherapy.

The study was designed to determine whether adding zoledronic acid to standard neoadjuvant therapy improved disease-related outcomes. The main endpoint was pathological response in the primary tumor.

Eligible patients received neoadjuvant chemotherapy (N = 206, 6.1%) according to local practice. They were randomly assigned to receive chemotherapy alone or zoledronic acid 4 mg IV three to four times weekly for six months in the neoadjuvant period in addition to chemotherapy. The primary surrogate endpoint for response was pathologically assessed residual invasive tumor size (RITS) at surgery.

All of the women had tumors larger than 50 mm (5 cm, or stage T3) or features of locally advanced disease (T4) or biopsy-proven lymph node involvement (stage N1). The patients were scheduled to undergo definitive surgery or radical radiotherapy, or both, with curative intent within six months of starting neoadjuvant therapy.

Among 188 evaluable women, the median RITS was 30 mm (3 cm) with chemotherapy alone and 20.5 mm (2.05 cm) with chemotherapy plus zoledronic acid. A multivariate analysis found a 14.1-mm difference in mean RITS with chemotherapy alone (42.4 mm, or 4.24 cm) and a difference of 28.2 mm with chemotherapy plus zoledronic acid (P = 0.002).

An analysis of the number of women achieving pathological complete response also revealed a significant difference favoring the addition of zoledronic acid: for chemotherapy alone, 5.8%, and for chemotherapy plus zoledronic acid, 10.3% (P = 0.03).

Finally, the proportion of patients requiring mastectomy was lower in those receiving chemotherapy plus zoledronic acid (65.3%) than with chemotherapy alone (77.9%). The combination was well tolerated, and no increase in serious adverse events was reported in the neoadjuvant treatment period.

"AZURE suggests a possible direct antitumor effect of zoledronic acid in combination with neoadjuvant chemotherapy and warrants a formal evaluation in prospective studies," Dr. Johnston concluded.

In an interview, lead author Dr. Winter said, “This is clearly exploratory and not practice-changing. Next, we are assessing biological effects in serial biopsies to see if there are changes in apoptosis and proliferation.”

RAD001 (Everolimus) in HER-2 Overexpressing Metastatic Breast Cancer with Prior Trastuzumab (Herceptin)

- Ruth O’Regan, MD, Emory University, Atlanta, Ga. (Paclitaxel)
- A. Fasolo, MD, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy (Vinorelbine)

Two early, multicenter clinical trials suggest that RAD001 (everolimus) may help overcome resistance to trastuzumab (Herceptin, Genentech) in women with HER-2–positive (HER-2+) metastatic breast cancer. It is thought that everolimus, an inhibitor of mammalian target of rapamycin (mTOR) signaling, acts on the pathway that mediates trastuzumab resistance and that it may help restore response in these patients.

Dr. O’Regan assessed weekly everolimus, combined with weekly trastuzumab and paclitaxel (Taxol, Bristol-Myers Squibb) among 27 women with disease that was resistant to trastuzumab. Trastuzumab resistance was defined as disease progression of three months or less after trastuzumab was given for metastasis or 12 months or less if it was given in a neoadjuvant setting. Most women had disease that was also resistant to taxanes. The median number of previous therapies was six.

Everolimus 5 mg and 10 mg daily or 30 mg weekly was generally well tolerated, but the investigators recommended 10 mg daily as the dose for further study. For 22 evaluable patients, Dr. O’Regan reported one complete response (5%), eight partial responses (36%), and stable disease in 11 patients (50%). The rate for disease control (i.e., complete response, partial response, and stable disease) for more than 16 weeks was 77%.

In another study, Dr. Fasolo evaluated weekly everolimus in 37 similarly trastuzumab-resistant patients receiving weekly trastuzumab and vinorelbine (Navelbine, GlaxoSmithKline). These patients had undergone a median of 4.5 previous regimens.
In the highest-dose everolimus arm, at 5 mg daily, dose reductions were frequent because of dose-limiting toxicities, including grade 3 and 4 neutropenia, grade 3 stomatitis, grade 3 fatigue, grade 2 dermatitis acneeform, and grade 3 anorexia. The most feasible dose was determined to be 30 mg weekly. For 34 evaluable patients, Dr. Fasolo reported one complete response (3%), five partial responses (15%), stable disease in 21 patients (62%), and disease control in 27 (79%).

Dr. O’Regan concluded, “Data presented at this meeting affirm the potential of RAD001 to reverse Herceptin resistance and to restore patient response to treatment.”

Lapatinib (Tykerb) plus Letrozole (Femara) or Letrozole Alone for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer

• Stephen Johnston, PhD, Royal Marsden NHS Foundation Trust, U.K.
• Carlos Arteaga, MD, Vanderbilt–Ingram Cancer Center, Nashville, Tennessee

First results from the EGF 2008 clinical trial evaluating letrozole (Femara, Novartis) plus lapatinib (Tykerb, GlaxoSmith Kline) in postmenopausal women with hormone receptor–positive (HR+) and HER-2+ metastatic breast cancer indicated that the combination was active as a first-line therapy. Dr. Arteaga, moderator of the meeting’s press conference, commented that the study was likely to have an impact on the standard of care for this population.

Endocrine resistance is associated with activation of the growth factor receptors epidermal growth factor receptor (EGF-R) and HER-2. Resistance to tamoxifen (Nolvadex, AstraZeneca) occurs in the presence of positive estrogen receptor (ER+) and HER-2+ status, and acquired expression of EGF-R/HER-2 may account for relapses. Complex crosstalk between EGF-R/HER-2 and ER pathways suggests that dual targeting may overcome endocrine resistance. Lapatinib, a small-molecule tyrosine kinase inhibitor (TKI) that blocks both EGF-R and HER-2, has demonstrated synergy with tamoxifen in models of endocrine resistance.

A randomized phase 3, double-blind, controlled trial enrolling 1,286 postmenopausal women with previously untreated ER+ and/or progesterone receptor–positive (PgR+) metastatic breast cancer (stage IIb/IIIc/IV) included a subgroup of 219 women with HER-2+ status. They were randomly assigned to receive letrozole 2.5 mg daily plus placebo or lapatinib 1,500 mg daily.

Median progression-free survival was three months for the women receiving letrozole/placebo and 8.2 months for those receiving letrozole/lapatinib. At 42 months, 82% of the patients had disease progression or had died in the letrozole-alone group, compared with 79% receiving the combination (hazard ratio [HR], 0.71, P = 0.019). The clinical benefit rate—complete responses plus partial responses plus stable disease at six months or more—in this population was 29% for letrozole/placebo and 48% for letrozole/lapatinib (P = 0.003). The overall response rates (complete and partial responses) were 15% and 28%, respectively (P = 0.021). Typical low-grade diarrhea and rash with the letrozole/lapatinib combination were treated by interrupting or reducing the dose or by managing adverse effects. Only nine patients had to discontinue treatment.

“The combination of letrozole and lapatinib offers a first-line orally active treatment approach for postmenopausal women with hormone receptor–positive, HER-2–positive metastatic breast cancer,” Dr. Johnston said.

He qualified his conclusion, noting that suitability for endocrine therapy is determined by the distribution of metastatic sites, performance status, and the absence of symptomatic or rapidly progressive visceral disease.

Sequential Letrozole (Femara) and Tamoxifen (Nolvadex) for Postmenopausal, Endocrine-Responsive Breast Cancer

• Henning Mouridsen, MD, PhD, Professor, Department of Oncology, Copenhagen University Hospital, Denmark

Updated results of the Breast International Group trial (BIG 1-98) suggest that for postmenopausal women with endocrine-responsive breast cancer, overall survival might be better with letrozole (Femara) than with tamoxifen (Nolvadex) and that women at high risk for early recurrence should receive first-line letrozole therapy.

Preliminary results of BIG 1-98, published in 2005, demonstrated that five years of first-line therapy with letrozole significantly prolonged disease-free survival (i.e., the time from randomization to the first occurrence of relapsing invasive breast cancer, invasive contralateral breast cancer, a second non-breast malignancy, or death from any cause) and reduced the risk of relapse in distant sites, compared with five years of initial tamoxifen therapy.

BIG 1-98, a multinational trial conducted in 27 countries, enrolled 8,028 women. These patients were randomly assigned to one of four treatment arms:

• tamoxifen for five years
• letrozole for five years
• tamoxifen for two years, followed by letrozole for three years
• letrozole for two years, followed by tamoxifen for three years

Other patients received monotherapy with tamoxifen or letrozole. The primary endpoint was disease-free survival.

Dr. Mouridsen’s presentation focused on letrozole and tamoxifen given in sequence, compared with letrozole alone (median follow-up, 71 months), and updated the comparison of letrozole alone with tamoxifen alone (median follow-up, 76 months). That latter comparison was complicated by the fact that after unblinding of the tamoxifen-alone arm, 619 patients (25.2%) selectively crossed over to letrozole monotherapy, mostly in the third to fifth years.

In the update of the monotherapy arms (N = 4,922), disease-free survival significantly favored letrozole (HR = 0.88, P = 0.03). A favorable trend was noted also in overall survival (HR = 0.87, P = 0.08). The time to distant recurrence significantly favored letrozole at the 0.05 level (HR = 0.85). Analyses censoring crossovers produced stronger letrozole-favoring hazard ratios (disease-free survival, 0.84; overall survival, 0.81; and
time to distant recurrence, 0.81, respectively).

Women in BIG-98 were randomly assigned to one of four arms, each with five years of treatment. In the analysis of 4,634 patients, with the authors testing whether a sequence of agents was superior to letrozole monotherapy, rates of five-year disease-free survival were similar for letrozole (87.9%), for letrozole followed by tamoxifen (87.6%), and for tamoxifen followed by letrozole (86.2%). However, in pairwise comparisons of tamoxifen first, followed by letrozole compared with letrozole alone, a trend favored letrozole alone for overall survival and time to disease progression. Comparing letrozole first, followed by tamoxifen versus letrozole alone, showed no significant differences for these parameters.

In a comparison of letrozole alone versus tamoxifen followed by letrozole at five years, letrozole alone was more favorable in terms of overall events (9.1% with tamoxifen, followed by letrozole, and 7.3% with letrozole alone).

Similar trends were found in an analysis according to nodal status: node-negative/positive for tamoxifen followed by letrozole was 14.7%/4.9% compared with letrozole (4.9%/3.5% for letrozole). Results for letrozole followed by tamoxifen and for letrozole alone, were “strikingly similar,” Dr. Mouridsen said (overall 7.3% for both and by nodal status 12.5%/12.4% for letrozole followed by tamoxifen/tamoxifen in node-positive women and 3.9%/3.5%, respectively, in node-negative women).

Dr. Mouridsen concluded that BIG-1-98 suggests superior overall survival with letrozole compared with tamoxifen in these patients. Adjuvant endocrine therapy should start with letrozole, especially in women at higher risk for early recurrence. Data on the sequential therapy also showed that women who did not tolerate aromatase inhibitor therapy after two years could be switched to tamoxifen.

**Zoledronic Acid (Zometa) and Aromatase Inhibitor–Associated Bone Loss in Postmenopausal Women with Early Breast Cancer Receiving Adjuvant Letrozole (Femara)**

- Holger Eidtmann, MD, University Frauenklinik, Kiel, Germany

Beyond confirming the prevention of bone loss with zoledronic acid, 36-month results of ZO–FAST (Zometa–Femara Adjuvant Synergy Trial) add to the accumulating evidence of the bisphosphonate’s antitumor effects.

Although the aromatase inhibitor letrozole (Femara) reduces recurrence risk in postmenopausal women with HR+ early breast cancer, it suppresses estrogen and is associated with accelerated bone loss and increased fracture risk. A 12-month analysis of ZO-FAST showed that the immediate use of zoledronic acid prevented bone mineral density (BMD) loss, and trial data from ABSCG-12 (the Austrian Breast and Colorectal Cancer Study Group) demonstrated bone loss prevention and improved disease-free survival.

Women in ZO-FAST (N = 1,064, median age, 57.5 years) were postmenopausal with HR+ early breast cancer. They received letrozole at a dose of 2.5 mg once daily for five years. Those with BMD T-scores of –2 or greater were randomly assigned to the immediate-zoledronic acid arm (IMZA). The remainder, in the delayed-zoledronic acid (DZA) arm, received zoledronic acid when either their post-baseline T-score decreased to below –2 or a nontraumatic fracture occurred. Zoledronic acid was given at 4 mg intravenously every six months.

The primary endpoint was the percentage of change in lumbar spine BMD at 12 months. A secondary endpoint was the time to disease recurrence or relapse.

At 36 months, the mean percentage of change in lumbar spine was +4.39 for the IMZA group and –4.9 in the DZA group (Δ9.29, P < 0.0001). Changes at the hip were +1.89 for the IMZA group and –3.52 for the DZA group (Δ5.41, P < 0.0001). Increases in the percentage of change were noted for both sites at 12, 24, and 36 months, but fracture rates at 36 months (5% for the IMZA arm and 6% for the DZA arm) were similar between groups.

The disease-free survival event risk was significantly lowered (41%) in the IMZA group (HR = 0.588, P = 0.0314). Adverse effects were similar in the groups except for one case of osteonecrosis of the jaw, which was reported in the IMZA patients. Of 532 patients (4.2%) in the IMZA arm, 22 experienced a local or distant recurrence, compared with 40 of 532 patients (7.5%) in the DZA arm. Even though differences in fracture rates between early and delayed administration were not significant, disease-free survival was significantly improved with initial zoledronic acid therapy.

Dr. Eidtmann concluded: “Immediate use of zoledronic acid prevents bone loss in women with early-stage breast cancer receiving adjuvant letrozole. ... The finding adds to the growing body of evidence that zoledronic acid can provide antitumor effects and may prolong disease-free survival in patients with early breast cancer.”

**MEETING HIGHLIGHTS: San Antonio Breast Cancer Symposium**