Emerging Trends in Breast Cancer Management

By Caroline Helwick

The most important scientific investigations in breast cancer are presented each year at the San Antonio Breast Cancer Symposium (SABCS). In its December 2009 meeting, several trends emerged, with strong implications to patient management and direct relevance to payers, patients, and providers.

Bisphosphonates: Not Just for Bone Loss Anymore

Bisphosphonates are now routinely given to postmenopausal breast cancer patients as a means of preventing bone loss associated with endocrine therapies (ie, tamoxifen and the aromatase inhibitors). As this class of agents matures, their efficacy in this setting (and their cost) is increasing. A growing body of data suggests that even the old-fashioned oral bisphosphonates may be protective not only against bone loss but also cancer.

Recent evidence indicates that bisphosphonates may have direct antitumor effects outside of the bone, according to Theresa Guise, MD, the Jerry W. and Peg S. Throgmartin Professor of Oncology at Indiana University School of Medicine.

Alison Stopek, MD, of the University of Arizona Cancer Center, Tucson, said that the investigational, fully humanized monoclonal antibody denosumab outperformed intravenous zoledronic acid (ZA) in preventing skeletal-related events (SREs). The study was an international phase 3 trial involving 2048 patients with metastatic breast cancer who were randomized to receive ZA or denosumab over 34 months.

SREs, such as fracture, occurred in 36.5% of the patients treated with ZA compared with 30.7% in those receiving denosumab, for a 6% absolute reduction in risk and a 16% relative risk reduction. Remaining on denosumab was also beneficial. Dr Stopek predicted that the data will continue to strengthen as patients are taking this drug longer.

The onset of moderate-to-severe pain was delayed with denosumab from a mean of 64 days to 88 days. Adverse event rates were similar.

Bone metastases are a significant problem for patients with certain types of cancers. The economic burden of bone metastases is estimated to be nearly $13 billion per year (Mundy GR. Nat Rev Cancer. 2002;2:584-593).

In October 2009, the US Food and Drug Administration rejected 2 of 6 applications for various indications for denosumab, asking for more data for its main indication—prevention of postmenopausal osteoporosis.

Zoledronic Acid Prevents Bone Loss. ZA was also effective in preventing bone loss in the Z-FAST (Zometa-Femara Adjuvant Synergy Trial) study of 602 patients taking the aromatase inhibitor letrozole. At 5 years, the patients who started taking the drug when their breast cancer treatment was initiated had a 6.2% bone mineral density (BMD) increase in lumbar spine area compared with a 2.4% decrease in BMD in those who delayed treatment until they had evidence of bone loss or fracture—an 8.6% total difference in efficacy.

“Women who are on Medicare tend to go with tamoxifen because the cost of an aromatase inhibitor puts them squarely in the doughnut hole of Medicare Part D, but once the cost barrier is removed there will likely be a mass switch to the aromatase inhibitor, which will necessitate the need for bone protection,” predicted Adam Brunfksy, MD, of the University of Pittsburgh Cancer Center, PA.

“There is a feeling among those of us who study these drugs that bisphosphonates of all kinds may actually prevent disease recurrence,” Dr Brunfksy said.

Prevention of Breast Cancer Recurrence? Bisphosphonates have also been accepted as having a protective effect on breast cancer recurrence, reducing the risk by 30% or more. This was powerfully shown in a recent study by Austrian investigators (Gnant M, et al. N Engl J Med. 2009;360:679-691) in which premenopausal patients who received intravenous ZA in addition to adjuvant endocrine therapy had a fairly unexpected, and highly significant, 36% relative reduction in risk of disease progression at 4 years.

James Ingle, head of breast cancer research at the Mayo Clinic Cancer Center, Rochester, called it a landmark study and “a reason for real enthusiasm.”

The study’s lead investigator, Michael Gnant, MD, of the Medical University of Vienna, suggested that bisphosphonates may squelch the population of tumor cells that migrate to the bone marrow to hide. This would affect the ability of the disease to recur, he said.

Primary Breast Cancer Prevention? Women taking bisphosphonates for bone health were 32% less likely to develop breast cancer than women not taking these agents, although the incidence of ductal carcinoma in situ was increased in bisphosphonate users by 59%. This could mean that in situ lesions are being arrested, preventing them from becoming invasive tumors, said author Rowan Chlebowski, MD, PhD, of...
Harbor-UCLA Medical Center, Los Angeles, whose study was based on the Women’s Health Initiative (WHI) cohort of 154,768 postmenopausal women.

This new analysis of the WHI showed that the subset of women using bisphosphonates, primarily alendronate, had a 31% lower rate of invasive breast cancer than those not taking them.

In an Israeli study of 4575 postmenopausal women, those taking oral bisphosphonates for ≥5 years had a 34% reduction in breast cancer incidence by self-reporting and a 28% reduction by pharmacy records, reported Gad Rennert, MD, PhD, of Carmel Medical Center, Haifa, Israel.

The cancer-reducing effect appeared after 1 year of bisphosphonate use. Cancers that developed in bisphosphonate users were more likely to have favorable characteristics, he said. However, “This is an association study, not a study of proof,” Dr Rennert pointed out. “We are raising a hypothesis.”

Other Strategies for Breast Cancer Prevention

Alcohol consumption of approximately half a mixed drink per day (a few drinks per week) raised the risk of recurrence by 34% and the risk of dying from breast cancer by 51% compared with less consumption. A study involving 1897 women from Kaiser Permanente in Oakland, CA, was presented by Marilyn Kwan, PhD, Kaiser Permanente Northern California.

Obesity (body mass index [BMI] ≥25 kg/m²) was associated with a 46% increased risk of distant metastases in 10 years and a 26% to 38% increased risk of dying from breast cancer. Women with a BMI ≥30 kg/m² responded poorly to chemotherapy or endocrine treatment compared with leaner persons. A study of 18,967 patients was presented by Marianne Ewertz, MD, from the Odense University Hospital, Denmark.

Treatment of Hormone-Positive Breast Cancer

In the 5-year results of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, the long-term benefit of exemestane was the same, whether it was given initially or after 2 to 3 years of tamoxifen. Disease-free survival at 5 years was 85% with either approach, reported Daniel Rea, MD, of the University of Birmingham, England.

Higher doses of fulvestrant may increase benefits without increasing toxicity, according to the international Comparison of Fulvestrant in Recurrent or Metastatic Breast Cancer (CONFIRM) trial. The approved dose is 250 mg per month, but 500 mg per month reduced progression by 20% without additional side effects, reported Angelo DiLeo, MD, of the Hospital of Prato, Italy.

Premenopausal women who become postmenopausal during hormonal treatment benefit from extended letrozole therapy after 5 years of tamoxifen, according to a substudy presented by Paul Goss, MD, of Massachusetts General Hospital, Boston.

Novel Agents for Metastatic Breast Cancer

BSI-210. For “triple-negative” breast cancer (negative for estrogen receptor, progesterone receptor, and HER2), which is hard to treat, the PARP inhibitor BSI-210 in combination with gemcitabine and carboplatin reduced breast cancer deaths by 50% in a study of 123 patients. The results, presented by Joyce O’Shaughnessy, MD, of Baylor Sammons Cancer Center, Dallas, TX, were called “spectacular” by the SABCS program committee.

T-DM1. A novel form of trastuzumab with a chemotherapy-like conjugate attached, significantly improved outcomes in 110 patients who had received an average of 7 prior treatments for metastatic disease. The drug produced responses or stable disease in 44%, a result called “remarkable” by outside specialists.

TKIs. For the oral multitargeted tyrosine kinase inhibitors (TKIs), findings were mixed. In the SOLT1-070 trial, sorafenib in combination with capecitabine reduced the risk of disease progression by 30% to 50% in all subgroups versus capecitabine alone, reported José Baselga, MD, of Vall d’Hebron University Hospital, Barcelona, Spain. William S. Gradishar, MD, Professor of Medicine at Northwestern University School of Medicine, Chicago, reported “a signal of potential activity” with sorafenib plus paclitaxel compared with the single-agent taxane, with a delay in progression of 1.3 months. Motesanib paired with paclitaxel was comparable with bevacizumab plus paclitaxel as initial metastatic treatment, although gallbladder toxicity was of concern with this new agent, reported John Mackey, MD, of the University of Alberta Cross Cancer Institute, Edmonton, Canada. In contrast, no benefit was found for sunitinib as a single agent in a Brazilian study of 482 patients.

MRI Better than Mammography in High-Risk Persons

Magnetic resonance imaging (MRI) detected breast cancer at an earlier stage than mammography in women deemed at high risk due to BRCA mutations, according to Ellen Warner, MD, of Sunnybrook Health Sciences Center, Toronto. The 1275 women in her study were screened with MRI plus mammography or with conventional mammography alone. MRI was more likely to detect early-stage and smaller tumors, suggesting that MRI should be part of screening for high-risk women.