

Treatment Updates From the Miami Breast Cancer Conference

BY DEBU TRIPATHY, MD

For 25 years, surgical and medical oncologists have gathered in sunny Miami to discuss the latest strategies in breast cancer management. At this year's meeting in March, a wide variety of topics, including new methods for treating inflammatory breast cancer and whether radiation therapy carries more benefit than risk for patients with small, invasive tumors, captured the interest of more than 1000 researchers and doctors.

Radiation Therapy Still Helpful in Patient with Small, Invasive Tumors

Several clinical trials have shown that radiation lowers the risk of breast cancer recurrence in patients who undergo breast-conserving lumpectomy for invasive breast cancer, and have established that lumpectomy plus radiation is an equally effective option compared with mastectomy for most patients diagnosed with early-stage breast cancer.

However, for very small cancers, the risk of recurrence in the breast after lumpectomy, known as a local recurrence, is very low, and radiation therapy does introduce short- and long-term side effects, such as hardening of the tissue, as well as the inconvenience of daily treatments for six weeks. Therefore, a clinical trial was designed for women with breast cancers of 1 centimeter or less who have negative lymph nodes to explore whether the use of tamoxifen alone could be as effective as radiation alone, and whether the two together might be better in preventing local recurrence.

Norman Wolmark, MD, chairman of the department of human oncology at Allegheny General Hospital in Pittsburgh, presented data of more than 1,000 women who were randomly assigned to one of three study arms—tamoxifen alone, radiation alone, or both tamoxifen and radiation. The percentage of patients who experienced a local recurrence over 10 years of follow-up was 19 percent with tamoxifen alone, 10 percent with radiation alone, and 5 percent with both tamoxifen and radiation.

These results confirm that radiation has a significant impact even with smaller tumors, and that tamoxifen lowers the risk further when added to chemotherapy plus radiation. Since most patients can be successfully treated with surgery for local recurrences, the mortality due to cancer spreading is very low with small node-negative cancers, and there was no difference in death rates among the treatment arms (in the 6 to 7 percent range for all three arms). However, this

study shows that we do not know of a lower size limit of invasive cancers for which one could spare radiation therapy to minimize the risk of local recurrence.

Finding the Optimal Agents and Sequence with Hormonal Therapy

Estrogen receptor-positive breast cancers, also called hormonally responsive disease, has historically been treated with the anti-estrogen drug tamoxifen, which can lower the risk of all recurrences by about half, as well as reduce risk of death due to cancer by about a third.

A newer class of drugs, aromatase inhibitors, blocks the formation of estrogen in postmenopausal women, and, in comparison to tamoxifen, leads to about 3 to 5 percent fewer recurrences. The design of the trials completed to date have varied, with the comparison arm being the standard five years of tamoxifen, and the investigational arm being either five years of an AI (upfront AI therapy), two to three years of tamoxifen followed by two to three years of an AI or the reverse sequence (both are considered “switching”), or five years of tamoxifen followed by 5 five years of an AI (extended therapy).

A summary of these trials, given by Hope Rugo, MD, of the University of California, San Francisco’s Helen Diller Family Comprehensive Cancer Center, clearly show that AIs are slightly better, with lower recurrence risk and lower distant recurrences (metastases). But no difference in survival has been seen yet, which some experts believe is due to the fact that the total number of deaths is rather low in general for hormonally responsive cancers in postmenopausal women.

Starting with an AI and then switching to tamoxifen or just using an AI for five years appears to be slightly better than starting with tamoxifen and switching to an AI, but the difference is not statistically significant.

In summary, these results point to superiority of an AI in some form. The optimal form of AI therapy (upfront or switching) is unclear, while the extended therapy option is somewhat out of favor because during the five years of tamoxifen there will be more expected recurrences compared with five years of an AI. And thinning of the bone, a side effect of AIs, might be less with the addition of tamoxifen.

Who Benefits from Adjuvant Taxane Therapy?

The use of taxane chemotherapy, such as Taxol (paclitaxel) or Taxotere (docetaxel), has been shown to lower the risk of recurrence for early-stage breast cancer by about 25 percent when added to standard chemotherapy, such as Adriamycin (doxorubicin) plus Cytoxan (cyclophosphamide). Some of the side effects, such as fatigue, neuropathy, and swelling, as well as rare allergic reactions, have raised the question as to whether taxanes should be used for everyone.

Earlier studies suggest that Taxol may be more effective in patients with hormone receptor-negative cancers and HER2-positive breast cancers. However, an

overview analysis of multiple trials that involved nearly 36,000 women showed that both taxanes lower the risk regardless of estrogen or HER2 receptor status.

Other protein and genetic markers are being examined to see if one can cull a group of patients that can be spared taxanes. One such protein, Tau, was initially believed to predict resistance to Taxol and sensitivity to tamoxifen based on the analysis of smaller trials. Analysis of the Tau protein in a large study comparing Adriamycin/Cytosan with or without Taxol showed that Tau was associated with estrogen receptor-positive, HER2-negative, and lower grade breast cancers, as well as better survival overall. However, Tau did not predict a differential response to Taxol or tamoxifen.

These results show that Tau cannot be used to help choose specific therapy such as taxanes, but after more confirmatory studies are done, it may help doctors determine if hormone receptor-positive cancers have a sufficiently good prognosis and if additional chemotherapy of any type could be spared. Better tests for sensitivity to specific chemotherapies represent an important area of ongoing research.

The Increasing Benefits of Oral Bisphosphonates

Several bisphosphonates, drugs that strengthen bone tissue, are approved for osteoporosis. And because aromatase inhibitors, a common treatment for hormone-positive breast cancer, can lower bone mineral density and increase the risk of fracture, studies have been done to assess whether bisphosphonates can protect bone tissue in patients undergoing these therapies. Several studies have shown the surprising result that these agents can actually lower recurrence risk, possibly due to direct tumor growth-inhibiting effects.

The Women's Health Initiative study was designed to test the effect of estrogen or estrogen plus progesterone replacement therapies on several health outcomes, including the risk of breast cancer. Interestingly, researchers found that estrogen plus progesterone—but not estrogen alone—increased the risk of breast cancer, and both regimens increased the risk of vascular events, including blood clots, heart attack, and stroke.

An exploratory analysis was carried out to see if women who took bisphosphonates for low bone mineral density had different risks of developing breast cancer. In contrast to hormone replacement therapy, the assignment of bisphosphonates was not randomized to patients in the trial; the information was captured with other health information and then analyzed.

Of the 154,768 participants, 2,816 were taking oral bisphosphonates at the beginning of the trial. There were 32 percent fewer invasive breast cancers in bisphosphonate users—3.29 compared with 4.38 per 1,000 patient-years (defined as the number of events seen during the equivalent of 1000 patients followed for 1 year)—which was statistically significant.

This is the first study to suggest a protective effect of bisphosphonates on breast cancer risk, and an exciting finding as another possible preventive agent for breast cancer. However, this study was not randomized and it is possible that the features that accompany low bone mineral density, rather than the

bisphosphonate itself, led to the risk lowering, so further studies are needed.

New Insights Into Inflammatory Breast Cancer

Inflammatory breast cancer is responsible for about 1 to 5 percent of all new breast cancer diagnoses in the United States and is more common in younger and African-American women. It has an aggressive behavior, and in the past was associated with a 90 to 95 percent mortality rate, which has improved significantly with the use of chemotherapy and biological therapy, including Herceptin (trastuzumab) for HER2-positive breast cancers, followed by surgery and radiation, with about 40 percent of patients now surviving.

IBC cells tend to have a higher grade and are more likely to be negative for hormone receptors and positive for HER2 protein overexpression—all markers of higher risk. It has recently been suggested from gene profiling studies that IBC and non-IBC are distinct biologic entities and may have differences in signaling pathways and angiogenesis, the formation of blood vessels to the tumor. There are specific proteins that give IBC a tendency to hone in on blood vessels in the skin, a feature that gives IBC its name owing to the redness and swelling in the skin over the breast. Clinical trials using newer HER2-targeting therapies, such as Tykerb (lapatinib) for HER2-positive IBC or the antiangiogenic agent Avastin (bevacizumab), show promising results with response rates higher than seen with conventional therapies.

The discovery of unique pathways, in addition to those driven by HER2 overexpression, has revealed many new targets for future trials. In addition, imaging tests such as MRI (magnetic resonance imaging) and PET (positron emission tomography) scans may be valuable tools to assess early response and to compare different drugs being evaluated in clinical trials. There is still much room for improvement in the early detection and better tailored treatment for this unusual variant of breast cancer.