Plenary Lecture #2: Adjuvant Bisphosphonate Therapy in Breast Cancer

M. Gnant, MD, FACS

Long used in the management of osteoporosis, bisphosphonate therapy eventually became a standard of care in the management of bone metastases to reduce skeletal events. In the adjuvant setting, bisphosphonates are used not only to mitigate the decreases in bone-mineral density, particularly associated with aromatase inhibitor therapy in patients with breast cancer but also to reduce the risk for bone metastasis more generally. It is this latter role that some studies have called into question—at least in the setting of breast cancer.

Early studies evaluating the effects of oral clodronate therapy showed mixed results: Some showed benefit in terms of reducing mortality and relapse rates, while others showed evidence of harm. Newer bisphosphonates such as zoledronic acid are considered to be more effective, but definitive data in support of their benefit with respect to preventing bone metastasis have been elusive.

When several trials, including ABCSG-12, ZFAST, and ZO-FAST, demonstrated reduced rates of relapse associated with bisphosphonate therapy in pre- and postmenopausal women with breast cancer, bisphosphonates seemed poised to become a new standard of care—that is, until the negative findings from the AZURE trial were published. That trial, along with mixed findings from other large clinical trials, rightly gave many clinicians pause about the continued use of bisphosphonates as adjuvant therapy in breast cancer.

So, is it possible to reconcile these discrepant findings? Dr. Gnant will argue that it is—namely, by looking at the estrogen environment. “When analysis is confined to women who are biologically postmenopausal or have been made postmenopausal by drugs that inhibit ovarian function, you see a consistent reduction in breast cancer relapse and improvements in overall survival [with bisphosphonates].”

Does the estrogen environment hold the key, determining whether bisphosphonate therapy is beneficial? The answer may be revealed this afternoon when Dr. Robert Coleman presents findings from a large meta-analysis (S4-07). Then, on Friday, Dr. Gunter von Minckwitz will report on results from the NATAN study (S5-05) of postneoadjuvant treatment with zoledronate in patients with tumor residuals after anthracycline-taxane–based chemotherapy for primary breast cancer.

Thursday, December 12th - 9:00 a.m.
Exhibit Hall D
Local Therapy: Is Less More?

This year’s William L. McGuire Memorial Lecture was presented by Dr. Monica Morrow. At scrutiny was local therapy in the molecular era, and the question was asked: How relevant is it? In particular, Dr. Morrow addressed two issues: margin width and management of the axilla—topics also covered by speakers during the Wednesday afternoon session.

Dr. Morrow, a surgeon, believes that we can leverage the benefits of decreased disease burden and systemic therapy to reduce the morbidity of local therapy (i.e., surgery). To make her point, she referred to a joint consensus statement (for which Dr. Morrow served as co-chair) by the Society of Surgical Oncology and the American Society for Radiation Oncology. With respect to margin width, the statement emphasizes that although negative margins are associated with optimal control, wider margin widths do not significantly improve local control, even in triple-negative breast cancer.

To address the issue of axillary management, Dr. Morrow drew from a 2011 paper in JAMA (Giuliano A et al), for which she was a coauthor. They found that, among patients with limited sentinel lymph node (SLN) metastatic cancer managed with breast conservation and systemic therapy, the use of SLN dissection alone was associated with survival outcomes as favorable as those seen with axillary lymph node dissection.

Data presented during the subsequent session continued on the topic of reducing unnecessary therapies. First, Dr. Ian Kunkler discussed the findings from the international trial known as PRIME2 (Postoperative Radiotherapy In Minimum-risk Elderly), which addressed the question of whether whole breast radiotherapy (WBRT) can be omitted in carefully defined groups of patients receiving appropriate systemic therapy. Dr. Kunkler presented the five-year data which show that, although WBRT is associated with a small but statistically significant absolute reduction in ipsilateral breast tumor recurrence, it does not appear to reduce the rate of regional recurrence, distant metastases, or overall survival.

Another topic of discussion during that session was the value or harm of resection and radiation of the primary site, even though metastasis has already occurred. As Dr. Rajendra Badwe pointed out during his presentation, data from preclinical and retrospective studies have been mixed: In some cases, the impact of locoregional treatment appears to be favorable, but others have found a signal of harm. In an attempt to

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Awards

AACR Distinguished Lectureship in Breast Cancer Research
Thursday, December 12, 11:30 am, Hall D

The AACR Distinguished Lectureship in Breast Cancer Research has been established to recognize outstanding science that has inspired or has the potential to inspire new perspectives on the etiology, diagnosis, treatment, or prevention of breast cancer.

The AACR Distinguished Lectureship in Breast Cancer Research has been established to recognize outstanding science that has inspired or has the potential to inspire new perspectives on the etiology, diagnosis, treatment, or prevention of breast cancer. This year, Dr. Michael R. Stratton is honored for his outstanding contributions to cancer research through groundbreaking contributions in the area of cancer genomics and genetics. Some of his major accomplishments include the discovery of the breast cancer susceptibility gene BRCA2 and somatic mutations of the BRAF gene in malignant melanoma and other cancers. He proposed the bold concept of a Cancer Genome Project that subsequently led to founding of the International Cancer Genome Consortium, which aims to sequence the genomes of thousands of human cancers in the next five to ten years. He led the group that mapped and identified BRCA2 at the Institute of Cancer Research (ICR) in London, UK. The breakthrough discovery of BRCA2 by Stratton directly transformed the lives of thousands of women in families with a history of breast cancer through predictive testing and prevention. Subsequent studies by his research team led to discovery of the first low-penetration breast cancer predisposition gene, CHEK2, followed by identification of additional low-penetration breast cancer predisposition genes, ATM, BRIP1 and PALB2 and the mapping and positional cloning of susceptibility genes underlying other types of cancer. Another major accomplishment of Stratton, and a major contribution to society, is the creation of the COSMIC (Catalog of Somatic Mutations in Cancer) database, the only comprehensive database with annotations of about 1,600,000 somatic mutations in cancer; gathered from scientific literature.

Signatures of Mutational Processes in Human Cancer
Michael Stratton, FMEDSCI FRS

Dr. Stratton studied medicine at Oxford University and Guy’s Hospital, specialized in histopathology and obtained his PhD at the Institute of Cancer Research, London. He is Director of the Wellcome Trust Sanger Institute, Hinxton, UK. He was awarded the 2010 Lila Gruber Cancer Research Award, the 2013 AACR GHA Clowes Award and the 2013 Louis-Jeantet Prize for Medicine. Stratton is an elected Fellow of the Royal Society and the European Molecular Biology Organization.
resolve these inconsistencies, his group conducted a prospective randomized trial to assess the impact of locoregional treatment on outcome in women with metastatic breast cancer at initial diagnosis. According to data presented by Dr. Badwe, locoregional treatment of the primary tumor did not result in any benefit in overall survival. In fact, surgical removal of the primary tumor may even encourage the growth of distant metastases—again adding to the argument that less is more.

Next, Dr. Atilla Soran presented early results of another trial with a similar objective—to assess whether early surgical treatment of the primary breast cancer in women presenting with stage-IV disease affects overall survival. The protocol differed from the previous trial in that locoregional therapy was performed before systemic therapy was instituted. (In the trial presented by Dr. Badwe, randomization to locoregional therapy or no locoregional therapy occurred after six cycles of anthracycline-based chemotherapy). Although the researchers found no statistically significant difference in overall survival, there did appear to be a trend that favored survival, especially in certain subgroups (namely, women with metastasis localized to the bones).

It seems that the improvements in systemic therapy have widely ranging implications—from a reduced benefit associated with screening mammography (as discussed in the morning by plenary speaker, Dr. H. Gilbert Welch) to the reduced need for surgery and radiotherapy and their associated costs and risk for adverse events.

### Tumor-infiltrating Lymphocytes as Prognostic Factors

Although breast cancer (BC) has not been traditionally considered as an immunogenic malignancy, a role for immune-targeted therapy is emerging. For example, worse clinical outcomes have been reported in transplanted (i.e., immunosuppressed) patients compared with non-transplanted patients despite no apparent differences in BC incidence between these two groups. Furthermore, tumor-infiltrating lymphocytes (TILs) have been consistently documented in BC lesions and have been associated with prognosis—an association explored by several presenters on Wednesday.

Dr. Sherene Loi presented findings from two trials: GeparQuattro and FinHER. The former is a prospective, single-arm, neoadjuvant cohort trial, which is evaluating the rate of pathologic complete response (pCR) in women with primary HER2-positive tumors treated with trastuzumab and chemotherapy (epirubicin/cyclophosphamide with docetaxel with or without capecitabine). In that study, high levels of TILs were associated with higher rates of pCR: For each 10% increment in TILs, the rate of pCR increased by 16%.

That there appears to be a positive association between the level of TILs and pCR has been suggested by numerous other studies, including FinHER. In fact, TILs have been described as predictive of response to neoadjuvant chemotherapy in BC and indicative of good prognosis after chemotherapy, especially in triple-negative BC. In line with these findings, Dr. Carsten Denkert presented data from the GeparSixto trial, which prospectively validated TILs as a predictive marker of response to neoadjuvant therapy with doxorubicin/taxane in triple-negative BC and HER2-positive BC. When carboplatin was added to therapy, the predictive value of TILs was even greater.

The focus on triple-negative BC was continued by Dr. Silvia Adams, who presented data...
from two phase-III breast cancer trials: ECOG 2197 and ECOG 1199. Both studies, which used contemporary adjuvant chemotherapy, show that stromal lymphocytic infiltration constitutes a robust prognostic factor in triple-negative BC. “The data,” asserts Dr. Adams, “provide strong evidence for the incorporation of this feature into routine histopathological assessment as a prognostic factor for patients with [triple-negative BC].”

But Dr. Lisa Coussens, discussant for the session points out a potential shortcoming of these and other studies: In evaluating the presence of TILs, standard histochemical studies of tissue sections does not distinguish different types of lymphocytes or myeloid cells. More specific data about cell types (as obtained by flow cytometry studies) may allow better patient selection for targeted therapy as well as identification of new targets to enhance tumor immune activity or inhibit immunosuppressive cells.

On a related note, Dr. Loi reported on the composition of TILs in tissue samples taken in the FinHER study and on the mechanism by which trastuzumab may mediate its anti-tumor effect. During her presentation, she stated that “Although further evaluation is needed, the data suggest that trastuzumab acts not only on the tumor directly but also may help anti-tumor activity.” She also suggested that the data “provide the rationale to evaluate whether a T cell checkpoint inhibitor, when added to trastuzumab, may further improve clinical outcomes in women with HER2-positive disease.

**Combination Blockade of the HER2 Pathway**

Two years ago at SABCS, researchers from the NeoALTTO study presented evidence that women with HER2-positive primary breast cancer (BC) benefited from dual HER2 blockade with trastuzumab and lapatinib, demonstrating a significantly greater rate of pathological complete response (pCR) than participants receiving either agent alone (51.3% for combination therapy, 29.5% and 24.7% respectively for trastuzumab alone and lapatinib alone). But do these benefits translate to long-term advantages in terms of disease-free survival (DFS) and overall survival (OS)? Based on NeoALTTO follow-up data presented by Dr. Martine Piccart-Gebhart on Wednesday, the answer is yes. At a median follow-up of 4 years, patients that achieved pCR had significantly better DFS and OS compared with those that did not achieve pCR. This association was observed in each of the three treatment arms and was particularly striking in women with hormone-receptor (HR)–negative tumors.

Dr. Piccart-Gebhart points out that the NeoALTTO study was not powered to detect moderate differences in survival among the treatment arms. Data addressing that question are expected to be presented by ALTTO trial investigators next year. However, the trends she presented suggest that dual HER2 blockade may be associated with superior benefit in terms of EFS and OS.

Although the survival data presented to date are promising, Dr. Piccart-Gebhart cautions that it would be premature to suggest that dual HER2 blockade be instituted as a new standard of care, in part because of increased risk for adverse events. She emphasizes that at this point “Even in [patients with] HR-negative cancer; the standard of care remains chemotherapy and trastuzumab.” However, the results of this trial may have another important implication—namely, the acceleration of the FDA approval process for new drugs. The FDA has initiated an accelerated approval process, which is based on a crucial assumption: that early benefit correlates with the long term effectiveness of a therapy. The data presented by Dr. Piccart-Gebhart support that assumption and may help pave the way to getting better drugs to more patients sooner rather than later.

Other presentations during the Wednesday morning session also discussed findings related to combination therapy with trastuzumab—either in the adjuvant or neoadjuvant settings. Dr. Sara Hurvitz reported findings from a phase II study evaluating the clinical and molecular effects of neoadjuvant docetaxel/carboplatin plus trastuzumab and/or lapatinib in HER2-positive BC. As other groups have shown using different chemotherapy backbones, combination HER2 blockade was associated with improved rates of pCR (the difference was statistically significant only when comparing combination blockade versus single blockade with lapatinib). Although combination blockade was not associated with an excess of cardiac events, it was associated with higher rates of other adverse events (most notably, diarrhea).

In the adjuvant arena, Dr. Dennis Slamon presented disappointing results regarding the addition of bevacizumab to chemotherapy plus trastuzumab. The failure of bevacizumab to improve outcomes may have been due in part to the high rates of DFS seen in the chemotherapy/trastuzumab arm, but nevertheless the poor performance likely represents one more nail in the coffin for bevacizumab.