Breast Cancer: Where are we now?

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49th Annual Meeting was held in Chicago, Illinois, USA, from May 31-June 4, 2013. The Meeting covered many interesting topics from all field of oncology

This symposium is designed to provide state-of-the-art information on the experimental biology, etiology, prevention, diagnosis, and therapy of breast cancer and premalignant breast disease to an international audience of academic and private physicians and researchers.

The most recent results were presented regarding the researching in molecular biology and the results of clinical studies for early stage and metastatic breast cancer.

Topics presented at meeting were interesting and highly up-to-date:

- Adjuvant Chemotherapy of Breast Cancer: Improving patients Selection and understanding Benefits and Risks
- Beyond Trastuzumab and Lapatinib: New Options for HER2-positive Breast Cancer
- Finding the balance in the Management of Low-Risk Breast Cancer
- Obesity and Inflammation: The Dangerous Duo in Breast Cancer
- Optimizing Locoregional Treatment in Early-Stage Breast Cancer
- Pushing the Limits of Upfront Care and Drag Development: Neoadjuvant Opportunities in Breast Cancer
- Surveillance and Monitoring in Breast Cancer Survivors: Maximizing Benefit and Minimizing Harm
- Treatment Algorithms for Hormone Receptor-Positive Advanced Breast Cancer

The topics were presented by leading oncology experts: Prof. Dr. Gabriel Hortobagyi, Martina Picart, Fatima Cordoso, Erica Mayer, David Cameron, Jose Perez - Garcia and others.

ADJUVANT THERAPY: WHICH PATIENT - WHICH REGIMEN?

Adjuvant chemotherapy improves outcomes in early breast cancer (EBC). However, as our understanding of breast cancer biology increases, and the choice of chemotherapy regiment broadens, two major questions are raised concerning adjuvant chemotherapy treatment decisions, namely: should my patient be receive chemotherapy? And if so, which is the best regiment?

In the past, treatment decisions regarding adjuvant chemotherapy in EBC were made solely based on clinic-pathological factors. However, with increased awareness of the importance of underlying tumor biology, we are now able to use genomic analysis to determine molecular breast subtype and thus identify patients with tumors that are chemotherapy resistant and unlikely to benefit from the addition of chemotherapy. Although genomic has allowed some patients to avoid chemotherapy-specifically those with Luminal A-like breast cancer-, these assays do not indicate which regiment is most appropriate. For this, consideration must be given to the combination of underlying tumor biology, tumor stage, and patient characteristics, such as age and tolerability of side effects. Here are some examples.

Triple-negative breast cancer (TNBC):

TNBC with good prognosis. TNBC is typical associated with poor prognosis; however, emerging molecular, clinical, and pathologic data indicate that the TNBC group is heterogeneous. In particular, histological special types of breast cancer – some of which are known to have excellent prognosis – are classified as TNBC. Of the 18 different histologist special types of breast cancer, at least four rare types – medullary, apocrine, metaplastic, and adenoid cystic carcinoma- are predominantly negative for ER, PgR, and HER2.Metaplastic carcinomas show worse prognosis compared with TNBC of no special type. Adenoid cystic and medullary carcinomas, despite the high proliferation index, have been consistently reported to have excellent prognoses. In the case of good prognosis TNBC, and absence of nodal involvement, adjuvant chemotherapy may be avoided. However, for node-positive disease, even of good prognosis subtype, adjuvant chemotherapy is recommended.

Other TNBC. Excluding the rare, good prognosis types, TNBC should be treated with chemotherapy, usually a sequential anthracycline/taxane regiment, especially in patients with node-positive disease. There is no data comparing a less intensive chemotherapy regiment with standard anthracycline plus taxane for lower- risk (pT1,pNo)TNBC; although consideration may be given to regimens such as TC or CMF, particularly if there was specific concern regarding treatment toxicities. Although excellent responses to cisplatin have been seen in patients with triple-negative, BRCA1-associated breast cancer, with pathologic complete response (pCR) rates of over 80%, pCR rates with cisplatin for sporadic TNBC are considerably lower, around 20%. Thus, platinum-based regiments are not recommended over standard adjuvant regiments in sporadic TNBC outside of a clinical trial.

CHEMOTHERAPY IN THE VERY YOUNG PATIENTS

Breast cancer in young patients (younger than age 35) is typically characterized by aggressive disease, including higher incidence of hormone-insensitive, undifferentiated, and HER 2 + tumors, and may be associated with unique biologic features compared with older women, while young age itself is an independent risk factor for poor prognosis.

Although luminal A-like EBC occurs less commonly in younger women than older, these tumors can be treated with endocrine therapy alone

(usually combined estrogen blockade), with excellent outcome expected. For Luminal B, HER2+, or TNBC, recommend use of adjuvant polychemiotherapy with an anthracycline plus taxane-based regimen, even for node-negative disease. Importantly, with all adjuvant breast cancer chemotherapy regimens being at least moderately gonadotoxic, young patients with EBC should have early referral to a reproductive specialist.

CHEMOTHERAPY IN OLDER PATIENTS

When considering adjuvant chemotherapy in older patients (age 65 or older) with breast cancer, the potential benefits from effective treatment must be balanced against risk of toxicities, functional decline, and decreased quality of life. Older women with biologically aggressive EBC may gain a much benefit from adjuvant chemotherapy as younger women; however, this specifically applies to fit elderly patients, with few, if any, comorbidities. Even in this selected group, increased toxicities from chemotherapy may be seen. The utility of adjuvant chemotherapy in older patients who are less fit is unknown. Authors recommended consideration of adjuvant chemotherapy for fit older patients with node-positive, HR-EBC, whereas chemotherapy may also be considered for HR+, luminal-B disease and node-negative, HR- disease. Based on superior outcomes with poliyhemotherapy, combination treatment is preferable to single agent therapy. Conversely, in patients who are frail and less fit, adjuvant chemotherapy outside of clinical trial setting is typically not recommended.

HER2+ BREAST CANCER

The standard adjuvant treatment of HER2+ EBC is trastuzumab plus chemotherapy, preferably using an anthracycline based regimen. However, only small percentage of patients receiving adjuvant anthracyclines actually benefits, yet all are exposed to the associated toxicities. In particular, the risk of cardiotoxicity is increased with sequential trastuzumab therapy. Thus, the mayor consideration in HER2+ EBC is whether to include an anthracycline in the treatment regimen.

The observed increased sensitivity of HER2+ tumors to anthracyclines may be related to coexpression of TOP2A.In the BCIRG-006 trial, both trastuzumab-containing arms (AC plus docetaxel/trastuzumab (ACTH) and docetaxel/carboplatin/trastuzumab (TCH) were superior to the non-trastuzumab arm of AC plus docetaxel (ACT),with the study not powered to detect a difference between ACTH and TCH. Benefit from anthracyclines evident in patients with TOP2A amplification. Numerous studies have also investigated the predictive role of TOP2A, with some evidence of utility, but as yet data are inconclusive.

Until the issue regarding the need for anthracyclines is resolved, choice of adjuvant chemotherapy regimen for HER2+ EBC should be based on clinical assessment of relapse risk. In the setting of high-risk features (pT>1 and/or pN>0), and anthracycline based regimen is reasonable. Conversely, lower- risk tumors could be treated with TCH. Alternative chemotherapy backbones to which anti/HER2 therapy may be added include TC or weekly paclitaxel; however, as these regiments have not yet been formally validated in randomized adjuvant trial, they should be used cautiously.

EARLY AND LATE LONG-TERM EFFECTS OF ADJUVANT CHEMOTHERAPY

Exposure to chemotherapy can lead to a variety of early and late long-term toxicities, including ovarian failure (with resultant infertility and sexual dysfunction), bone loss, weight gain, neurotoxicity, neurocognitive changes, cardiac toxicity, and secondary malignancy. All effects have potential to lead to a decrease in quality of life and a decrement on overall health status. The etiology of this complication is thought to reflect exposure to topoisomerase II- targeted agents (anthracyclines) or alkylating agents (cyclophosphamide), which are frequently included in adjuvant chemotherapy regimens. The risk of secondary malignancy appears to reflect increased cumulative dose exposure, although most series report population rates of less than 1%.

Older patients are thought to be at increased risk of myeloid complications, although they have typically been excluded from analysis of younger cohorts who participate in clinical trials.

Method to reduce exposure to potentially bone marrow-toxic chemotherapy may help reduce risk of secondary myeloid malignancies. Adjuvant regimens, which replace anthracycline with a taxane, have demonstrated slightly decreased rates of secondary myeloid malignancies.

Improved management of the effects of chemotherapy will require better understanding of management strategies, and larger prospective trials evaluating a variety of interventions are underway. Additionally, for the first time, the 2013 NCCN Guidelines will include guidelines for screening breast cancer survivors for many of the common short and long-term effects from therapy. After decades of recognition of many of the detrimental effects of treatment, it is hoped that future clinical and research activities will definitively reduce adverse therapy-related outcomes for breast cancer survivors.

OBESITY AND INFLAMMATION: THE DANGEROUS DUO IN BREAST CANCER; NEW INSIGHTS INTO BREAST CANCER DEVELOPMENT AND PROGRESSION

The importance of inflammation in promoting carcinogenesis and tumor progression is well recognized. Chronic inflammation caused by a variety of infectious agents can lead to the development of several common malignancies. Much less is known about the link between inflammation and the development of breast cancer. Recent data suggest that obesity causes both in-breast and systemic inflammation that contribute to the development and progression of breast cancer. In postmenopausal women, the risk of developing breast cancers that express the estrogen and progesterone receptors (ER and PR),is significantly elevated for those who are obese or overweight. After menopause, estrogen is mostly derived peripherally from the noncyclical conversion of androgen precursors within adipose tissue. Circulating estrogens, such as estradiol, are known to stimulate the proliferation of breast epithelial cells and potentially exert a mutagenic effect. Higher levels of circulating estradiol as a result of increased adiposity and aromatase expressions are thought to contribute, in part, to the greater risk of ER/PR-positive breast cancer in obese postmenopausal women.

Additional evidence suggests that there are likely to be several estrogen-independent mechanisms involved in the link between obesity and breast

carcinogenesis. In addition to the elevated risk of hormonally sensitive breast tumors, obesity has also been associated with an increased risk of ER-negative breast cancers in some studies. Obesity is associated with chronic, systemic inflammation characterized by elevated levels of circulating proinflammatory mediators known to promote tumorigenesis and growth. Both the systemic and local consequences of chronic adipose inflammation thus provide key potential mechanistic links between obesity and breast cancer. In addition to inflammation, other obesity-related effects promote cell proliferation and survival.

OBESITY AND ITS IMPACT ON BREAST CANCER: TUMOR INCIDENCE, RECURRENCE, SURVIVAL, AND POSSIBLE INTERVENTIONS

Obesity has been associated with cancer risk and mortality. Cancers associated with obesity according to meta-analysis studies: breast, colon, endometrial, esophageal adenocarcinoma, gallbladder, leukemia, multiple myeloma, non-Hodgkin lymphoma, pancreas, renal, thyroid, and possibly ovarian cancers.

Obesity is associated with breast cancer incidence and prognosis, and increasing evidence implicates sex hormones, insulin, adipokines, and their inter-related biologic pathways as major factors underlying these relationships. More importantly, these hormones and biologic pathways represent important potential targets for primary and secondary breast cancer prevention. Several lifestyle intervention trials have been conducted in breast cancer survivors, demonstrating the feasibility of implementing weight loss and other interventions after cancer diagnosis. Data from two large-scale dietary intervention studies provide further evidence that dietary changes that produce weight loss may improve outcomes in breast cancer survivors, and other studies suggest that weight loss induces significant favorable changes in biomarkers linked to breast cancer risk and outcomes. Adequately powered adjuvant studies are needed to define the role of weight loss in the management of overweight and obese breast cancer survivors. Overall, the association of obesity with breast cancer incidence and prognosis represents a very significant, but still under-exploited opportunity to improve prognosis for patients with early-stage breast cancer.