The New Millennium for Adjuvant Therapy in Breast Cancer

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The treatment of microscopic metastatic breast cancer with adjuvant systemic therapy has undergone significant changes in recent years. At the same time, our understanding of the biology of breast cancer has also improved, predominantly as a consequence of data obtained from cDNA microarrays.

This issue of ONCOLOGY is devoted to the memory of Dr. Martin Abeloff of Johns Hopkins University. Marty Abeloff was many things: a superb cancer researcher with a broad range of scientific interests, the director of one of the nation’s great cancer centers who oversaw its enormous growth, and a charming and decent human being who was loved and respected by all who knew him. He was also a spectacular mentor of junior faculty, both inside and outside of his institution. I came to know Marty when I joined the Breast Cancer Committee of the Eastern Cooperative Oncology Group, which he ably led in the late 1980s and early 1990s. His care for junior faculty deserves special comment. He considered them colleagues, to be respected and nurtured. He was a great listener who always seemed to have time for the often-naive thoughts of unseasoned juniors. I learned a great deal from him, and it is a matter of real sadness that I will not be able to share any more time with him.

Adjuvant therapy for breast cancer has changed immensely since the early 1990s, and these changes are the subject of this review. The research interests of those times are strikingly different from those of today. The dominant questions then being asked focused on questions of chemotherapy technique—in essence, how much drug could be administered, and did alterations in dose, dose intensity, or dose density affect outcome.

The questions of the new millennium reflect a strikingly different focus: How can our burgeoning understanding of the biology of breast cancer influence therapy? A related question suggests how far we have come from the 1990s: “Who doesn't require treatment?” This review will examine the new biology of breast cancer and its therapeutic implications for adjuvant therapy.

The New Biology of Breast Cancer

Perhaps the most profound changes in our approach to adjuvant therapy in the past decade have been driven by changes in the understanding of breast cancer biology. In the not-too-distant past, breast cancer was viewed from a therapeutic standpoint as being essentially a single disease. While differentiations were made between estrogen receptor (ER)-positive and -negative breast cancer for the purpose of administering hormonal therapy, in essence all patients were considered potential candidates for cytotoxic chemotherapy. This therapeutic consensus, a legacy of population-based adjuvant trials of the 1980s, was formalized at the National Institute of Health’s 2000 Consensus Development Conference on adjuvant therapy for breast cancer. The conference panel recommended consideration of adjuvant chemotherapy for essentially all patients with tumors greater than or equal to 1 cm in size.[1]

At the same time that the Consensus Conference was advising physicians and patients, the Human Genome Project was using novel technology to revolutionize our understanding of the human genome. Spinoff technologies such as cDNA microarrays (“gene chips”) allowed investigators to examine large portions of the human genome in human breast cancers. Analysis of the results both reaffirmed and altered our understanding of breast cancer—reaffirmed, because genomic analyses suggested that some of our therapeutic interventions (such as hormonal and HER2-targeting therapy) had a solid basis in the cancer cell’s genetic makeup; altered, because it became clear that breast cancer should be considered a collection of diseases rather than a solitary disease. Breast cancer is now best thought of as a group of criminals sharing the same boarding house, requiring different forms of apprehension and punishment.
In broad terms, genomic analyses suggest the existence of luminal tumors (with at least two subtypes, A and B), which encompass the estrogen-sensitive breast cancers; basal tumors, which are in large part estrogen-, progesterone-, and HER2-negative; and c-erbB2-positive, ER-negative tumors.[2-4] Breast cancer therapies largely parallel these subtypes: Hormonal manipulations are most likely to benefit luminal A tumors, many luminal B cancers benefit from chemotherapy, triple-negative (basal) tumors are currently best treated with chemotherapy, and c-erbB2-positive (HER2-positive) tumors benefit from HER2-targeting therapy. Systemic adjuvant therapies increasingly appear to have focused benefits related to genomic categories.

### Treatment of Luminal Breast Cancers

As mentioned above, a significant proportion of human breast cancers fall into the broad general category of luminal cancers. These cancers are typically ER-positive. By the mid-1990s it had become apparent to clinical investigators that the use of adjuvant hormonal therapies (tamoxifen in pre- and postmenopausal women, and ovarian ablation in premenopausal women) provided significant, if incomplete, benefits with regard to disease-free and overall survival in both lymph node-negative and -positive disease. Similarly, trials randomizing patients with ER-positive tumors to hormonal therapy alone or hormonal therapy plus chemotherapy suggested that the addition of adjuvant chemotherapy improved disease-free and overall survival, though generally with modest overall benefits and not insignificant risks.[5]

New genomic analyses provide an intellectual basis for these empirical findings. Women with luminal A breast cancers (as variously defined by investigators using a variety of clinical assays)[6] have both a good overall prognosis and a high likelihood of benefit with hormonal manipulations (and, conversely, a low likelihood of benefit with cytotoxic agents). This is particularly true for patients with lymph node-negative tumors, where commercially available clinical assays (eg, OncotypeDx and Mammaprint) now play an established role in determining chemotherapy benefit.[7-10]

Recent genomic data from the Southwest Oncology Group (SWOG) 8814 trial suggest that lymph node-positive luminal A tumors may derive little or no benefit from the use of cytotoxic therapy when compared to the use of hormonal therapy alone.[11] In contrast, women with non-luminal A ER-positive tumors appear to derive significant benefit from the use of adjuvant chemotherapy, and may receive less benefit from the use of adjuvant hormonal therapy.[8] These tumors (currently commonly called luminal B, though other subtypes may exist) are characterized by a proliferative gene signature, and in many cases are both ER-positive and HER2-positive.

While the use of hormonal therapies for luminal cancers is well established, which hormonal therapies should be used (and how they should be used) remains a matter of controversy, or at least uncertainty. Until the current decade, the selective estrogen receptor modulator tamoxifen represented the standard of care for ER-positive postmenopausal tumors. In recent years numerous prospective randomized controlled trials comparing tamoxifen to any of three commercially available aromatase inhibitors (anastrozole [Arimidex], letrozole [Femara], and exemestane [Aromasin]) have demonstrated statistically significant improvements in disease-free survival for aromatase inhibitor therapy. These trial results led to new guidelines by the American Society of Clinical Oncology, suggesting that aromatase inhibitor therapy should represent part of the standard of care in all postmenopausal women with ER-positive breast cancer.[12]

Overall survival benefits have proved lacking in many aromatase inhibitor trials, including the one with the longest overall follow-up.[13] These benefits are accompanied by an altered toxicity profile, with aromatase inhibition being associated with decreased rates of gynecologic and thromboembolic toxicities, and increased rates of musculoskeletal complaints and decreased bone mineral density. These altered toxicity profiles are often important for individual patients in the clinic, and to some extent may affect treatment decisions.

### Unresolved Questions

Numerous questions remain regarding hormonal therapies, which represent the basis of ongoing clinical trials. These may be summarized as follows:
(1) Given that aromatase inhibitor therapy should represent a standard therapy for postmenopausal women, when should it be administered? Clinical trials have examined aromatase inhibition as initial therapy, as crossover therapy (typically after 2 to 3 years of tamoxifen), and as maintenance therapy following tamoxifen. Benefits in all three settings have been observed.[12] Is any approach preferable?

(2) Should premenopausal women receive tamoxifen alone, tamoxifen plus ovarian ablation, or ovarian ablation plus aromatase inhibitor therapy? These questions are currently being addressed in the international Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT).

(3) How long should adjuvant hormonal therapy be administered? Early trials suggested that 5 years of adjuvant hormonal therapy with tamoxifen should represent the standard of care. More recent data from the Adjuvant Tamoxifen, Longer Against Shorter (ATLAS) trial has suggested that longer durations of adjuvant tamoxifen might offer disease-free survival benefits over 5 years of therapy, and the Canadian MA.17 trial (comparing maintenance aromatase inhibitor therapy to placebo following 5 years of tamoxifen) suggested a significant benefit for prolonged hormonal therapy.[14] Although trials examining this question about aromatase inhibitor therapy are ongoing, we currently have no data regarding the optimal duration of such therapy.

**HER2-Targeting**

HER2-positive breast cancers represent a biologically distinct population of tumors characterized by increased cell proliferation, invasion, and metastasis. Late in the past decade, evidence emerged in the metastatic setting demonstrating a survival benefit for targeting the HER2 receptor with the humanized monoclonal antibody trastuzumab (Herceptin).[15] This important finding, in turn, led to the development of several adjuvant trastuzumab trials for women with HER2-positive tumors.

Initial reports of these trials in 2005, as well as subsequent reports, clearly demonstrated that HER2-targeting significantly improves both disease-free and overall survival in the adjuvant setting.[16-18] This was true whether HER2-targeting occurred with or following chemotherapy, in both lymph node–negative and lymph node–positive disease, and in the context of both anthracycline- and non–anthracycline-based regimens. The use of adjuvant trastuzumab rapidly became a new standard of care in HER2-positive tumors.

**Unresolved Questions**

As with the use of adjuvant hormonal therapies, HER2-targeting has many unresolved questions. A brief (and no doubt incomplete) summary of these questions include:

(1) What is the appropriate duration of adjuvant HER2-targeting? While the initial large phase III trials routinely administered a year of adjuvant trastuzumab, a smaller trial (the FinHer trial) appeared to demonstrate a similar degree of benefit with a far shorter duration of therapy.[19]

(2) Should adjuvant trastuzumab-based therapies be administered in the context of anthracycline-based therapy? Many HER2-positive tumors coamplify topoisomerase II-alpha, the principal biologic target for anthracyclines, and clinical data from pretrastuzumab adjuvant trials suggest that the preferential benefit of anthracycline-based chemotherapy seen in adjuvant trials is restricted primarily to women whose tumors coexpress HER2 and topoisomerase II-alpha.[20] At the same time, the use of adjuvant trastuzumab in the context of anthracycline-based adjuvant therapy appears to be associated with a greater risk of congestive cardiomyopathy, and (in the Breast Cancer International Research Group [BCIRG] 006 adjuvant trastuzumab trial) without demonstrably superior benefit compared to a non–anthracycline-based regimen.[21]

(3) Should adjuvant trastuzumab be used in combination with or following adjuvant chemotherapy in patients requiring adjuvant chemotherapy? Adjuvant trastuzumab has shown clinical benefit in both settings. The North Central Cancer Treatment Group (NCCTG) N9831 trial, in its initial reporting, suggested that concurrent therapy was superior to sequential therapy. A more mature analysis of this trial awaits further follow-up.
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(4) How low should we go? There is vanishingly little data on the use of adjuvant HER2-targeting for tumors <1 cm in diameter and, indeed, little information on the prognosis of such tumors in the absence of adjuvant trastuzumab.

(5) What additional benefit will be obtained from the addition of novel HER2-targeting agents to adjuvant trastuzumab? Novel receptor tyrosine kinase inhibitors of the HER family (such as lapatinib [Tykerb], which targets HER1 and HER2), as well as novel agents targeting the extracellular membrane domain of HER2 (e.g., pertuzumab, which prevents receptor dimerization), are under development.[22] Will such agents add benefit in the adjuvant setting?

Triplet-Negative Breast Cancer

Adjuvant chemotherapy represents the only currently available adjuvant systemic therapy for women with triple-negative (basal) breast cancers, and as suggested above represents a mainstay of therapy for non-luminal A and HER2-positive breast cancers as well. The past decade has seen the introduction and exploration of the taxanes in the adjuvant setting. Currently the standard of care for lymph node–positive tumors represents the use of anthracycline- and taxane-based combinations. Data generated by The Breast Cancer Intergroup (TBCI) over the past decade suggests that the use of dose-dense (every-2-week) chemotherapy, or of weekly paclitaxel, are associated with improved disease-free and overall survival.

Unresolved Questions

As with estrogen- and HER2-targeting therapies, the use of adjuvant chemotherapy remains in flux, with numerous unanswered questions. These include the following:

(1) Should anthracyclines be used in non–HER2-positive (or non–topoisomerase II-alpha–positive) breast cancers? As mentioned above, current data suggest that the preferential benefit of anthracyclines may be limited to women with HER2-positive (or topoisomerase II-alpha–positive) breast cancers.[20] If this is indeed the case, should any population of non–HER2-positive tumors be treated with anthracycline-based therapies?

(2) If non-anthracyline-based therapies are to be used for non–HER2-positive tumors, which regimens should be used? Many of our current standard regimens (e.g., dose-dense combinations of doxorubicin, cyclophosphamide, and docetaxel [AC→T and TAC]) contain anthracyclines, and have not been compared to nonanthracycline regimens. The theory of “dose-densification,” for instance, was tested and shown to have a survival benefit in the context of anthracycline-based therapy.[23] The comparison of TC (docetaxel [Taxotere]/cyclophosphamide) to AC (doxorubicin [Adriamycin]/cyclophosphamide) demonstrated the superiority of the nonanthracycline regimen (TC),[24] but AC hardly represents a standard of care for lymph node–positive breast cancer. Is TC a worthy substitute for TAC or AC→T?

(3) Should novel chemotherapeutic approaches be considered for triple-negative (basal) breast cancers? Basal cancers represent the natural genomic “home” for BRCA1-mutant breast cancers, and recent evidence suggests that such cancers may be preferentially sensitive to DNA-damaging chemotherapeutic agents (e.g., platinating agents). Should the use of DNA-damaging regimens be specifically studied in such patients? Similarly, novel DNA-damaging biologic agents (e.g., polymerase [PARP] inhibitors) are currently undergoing therapeutic trials in the metastatic setting for basal (especially BRCA1-mutant) breast cancers.

Novel Therapeutic Targets in the Adjuvant Setting

While the standard therapeutic approach to the systemic therapy of breast cancer has involved attacks on the cancer cells in human tumors, it is increasingly clear that the tumor microenvironment plays an important role in breast cancer growth, invasion, and metastasis. In recent years, therapies targeting the tumor microenvironment have entered the routine treatment of metastatic breast cancer. We are now beginning to see the movement of these therapies into the adjuvant setting.
The first such agents were the bisphosphonates. Bisphosphonates have long been a mainstay of therapy for patients with bony metastatic disease, where their use has demonstrated clinical benefits with regard to prevention of skeletal-related events such as bone pain and fracture. Preclinical data suggested that bisphosphonate therapy might also serve a role in the prevention of micrometastatic bony disease. This led to the development of clinical trials investigating bisphosphonate therapy in the adjuvant setting. An initial generation of trials—not large studies by current standards—suggested that adjuvant bisphosphonate therapy might prevent the development of bony metastatic disease. This, in turn, has led to the development of larger adjuvant trials, the results of which are anxiously awaited.

A newer approach to targeting the tumor microenvironment in the adjuvant setting has involved the use of antiangiogenic therapies. Numerous antiangiogenic therapies are in development for a variety of human cancers, and three such agents have been approved by the US Food and Drug Administration (FDA) for the treatment of a variety of cancers (including renal, colorectal, lung, hepatic, and breast cancers).

In breast cancer, the agent with the greatest database in the metastatic setting is bevacizumab (Avastin), a humanized monoclonal antibody developed against vascular endothelial growth factor (VEGF). This agent was recently approved by the FDA for the treatment of metastatic breast cancer, based on a randomized controlled phase III trial comparing paclitaxel with paclitaxel plus bevacizumab as first-line therapy for metastatic breast cancer. Based on the results of this trial, adjuvant therapy trials have been initiated for early-stage breast cancer.

Conclusions

Adjuvant systemic therapy for breast cancer has undergone profound changes in the past decade, based in large part on our improving understanding of the biology of breast cancer. In the coming years, we will no doubt continue to see improvements in the treatment of microscopic metastatic disease as we explore novel biologic therapies in the context of existing systemic therapies. It also seems likely that we will continue to improve the selectivity of adjuvant therapy, as the use of genomics and other technologies (eg, proteomics and pharmacogenomics) further hasten therapeutic individualization.

While breast cancer remains an all-too-frightening disease, it is not unreasonable to suggest that the next decade will bring therapies that are both safer and more efficacious for women with breast cancer. If so, we can be sure that Dr. Martin Abeloff would have been proud of what his research descendants have accomplished.

This article is reviewed here:
Making Strides in Adjuvant Therapy for Breast Cancer
Adjuvant Therapy for Breast Cancer: Current Approaches and Strategies for a Better Future

References


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