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Past, Present, and Future Challenges in Breast Cancer Treatment

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The past half century—the lifetime of the American Society of Clinical Oncology—represents a historical watershed in the management of breast cancer, a period in which old dogmas were overthrown, to be replaced by biology-driven therapeutic approaches. These approaches transformed the disease from one where mutilating local therapy was followed by distant recurrence and death, to one where patients regularly choose local (and often minimal) therapy, then receive systemic therapies that are increasingly effective and progressively more targeted.

Breast cancer, perhaps more than any other solid tumor, was transformed by the progressive application of clinical hypothesis testing of basic biologic concepts. The revolutionary overthrow of the Halstedian hypothesis, with its emphasis on the primacy of locoregional control through extensive surgery, led to changes both in locoregional therapy as well as providing the intellectual basis for adjuvant systemic therapies. And, at a time when systemic therapies were dominated by rank empiricism, breast cancer led the way in the application of targeted biologic therapy, long before targeted therapy became an oncologic mantra.

This article will review a half-century of progress, focusing on the areas in which the greatest progress has been seen: the revolution in locoregional therapy; the application of cytotoxic chemotherapy in both local and advanced disease; the discovery and therapeutic exploitation of estrogen receptor biology; the use of estrogen receptor biology for breast cancer prevention; and the targeting of the human epidermal growth factor receptor complex. Collectively, these constitute a revolution in breast cancer therapeutics that has occurred within the lifetime of an organization. Finally, we will touch on the remaining therapeutic challenges for this disease.

Locoregional Therapy

The locoregional treatment of breast cancer has been transformed through changes in both the biologic understanding and the clinical presentation of the disease. Starting with the pivotal randomized clinical trials from the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Milan group, radical mastectomy was replaced by modified radical mastectomy and eventually breast-conserving surgery, with breast radiation becoming the preferred method of locoregional management in appropriate candidates.[1] Increasing adoption of breast-conserving surgery was documented in the 1990s, and the rates of breast conservation became a quality indicator for breast cancer programs.

More recently, a trend towards increasing use of mastectomy (both unilateral and bilateral) has occurred in the United States.[2] This trend results from improvements in mastectomy techniques and reconstructive options and increasing use of genetic testing and preoperative breast MRI, as well as patient-related ethnic, social, and cultural factors.[1,3] This increase occurred even as local recurrence rates following breast-conserving surgery dropped dramatically, the result of improved surgical and radiation therapy techniques as well as advances in adjuvant systemic therapy.[4]

The recognition of the biologic significance of locoregional recurrence as an indicator rather than an instigator of increased risk for distant disease[4-6] was an important step in better understanding breast cancer biology with significant clinical implications.[7] Systemic chemotherapy at the time of locoregional recurrence was formally evaluated in a recent randomized clinical trial that demonstrated significant improvement in disease-free survival and overall survival for this poor-prognosis group.[8]

Lymphatic mapping and sentinel lymph node biopsy,[9-11] important advances in breast cancer surgery, successfully challenged the primacy of axillary lymph node dissection for axillary staging, first in patients with negative sentinel lymph nodes[10] and more recently in patients with limited sentinel lymph node involvement (one to two involved nodes or nodes involved by micrometastases).[12,13] This approach reduced morbidity while providing adequate staging information and outstanding local control in the axilla. Remaining questions with sentinel lymph node biopsy include the adequacy of sentinel lymph node biopsy alone in mastectomy patients with positive sentinel lymph nodes and in patients with positive sentinel lymph nodes following neoadjuvant chemotherapy.

Neoadjuvant (preoperative) chemotherapy for locally advanced and operable breast cancer has been a major development with important implications for locoregional management.[14] On the basis of the results of several nonrandomized and randomized clinical trials,[15-19] neoadjuvant chemotherapy has become the standard of care for patients with locally advanced breast cancer and a reasonable alternative to adjuvant chemotherapy with large operable disease.

Although the initial impetus for neoadjuvant therapy was provided by the desire to convert patients with inoperable tumors to operable mastectomy candidates, and those who were mastectomy candidates to candidates for breast-conserving surgery, more recently the focus has been in the potential downstaging of axillary nodes with resulting reduction in the extent of axillary surgery and in the potential tailoring of postoperative radiotherapy. Accurate assessment of the location and extent of the primary breast tumor and axillary nodes before, during, and after neoadjuvant chemotherapy remain important challenges.

In coming years, the development of more active neoadjuvant chemotherapy regimens and novel molecular and imaging techniques will undoubtedly lead to additional individualization of locoregional management, including the real possibility of avoiding formal surgical resection of the primary tumor and axillary nodes in patients who have high likelihood to have achieved a pathologic complete response. Recently, the Food and Drug Administration accepted the use of pathologic complete response in the neoadjuvant setting as a biomarker for therapeutic benefit and accelerated drug approval, a policy shift with major implications for new drug development.

The demonstration of an association between genomic profiling/molecular subtyping and locoregional recurrence is an exciting development, and several seminal papers on the subject have been published in *Journal of Clinical Oncology*.[20-25] This is a promising approach for further individualizing locoregional management.

Chemotherapy and Triple-Negative Breast Cancer

By the 1960s, several combinations of cytotoxic agents had been proposed and tested.[26] The five-drug Cooper regimen became quite popular because of its high response rate.[27] Doxorubicin was introduced into clinical trials in 1967 and by the early 1970s was considered the most effective agent against breast cancer.[19,28] Anthracycline-based combinations with cyclophosphamide followed (doxorubicin plus cyclophosphamide, as well as fluorouracil, doxorubicin, and cyclophosphamide), and combination chemotherapy became the standard of care in both the metastatic and adjuvant setting.[29] Sporadic reports of the significant activity of platinum salts in previously untreated metastatic breast cancer were largely ignored.[30,31] Many new cytotoxic agents were developed and tested during the 1970s and 1980s, but none had a satisfactory therapeutic index. The development of the taxanes represented a major milestone in the systemic therapy of breast cancer, with both paclitaxel and docetaxel showing activity similar to and sometimes exceeding that of the anthracyclines.[32] Randomized trials demonstrated at this stage that anthracycline-containing regimens were somewhat superior to regimens not containing an anthracycline.[33]

Simultaneously, the routine use of combination chemotherapy for patients with metastatic breast cancer began to be questioned.[34] A large randomized trial comparing single-agent doxorubicin to single-agent paclitaxel and to the combination of both agents indicated that the combination produced higher response rate and longer time to treatment failure, but no difference in overall survival.[35] This study and meta-analysis of other controlled trials turned the tide, and the standard of care became again sequential single-agent chemotherapy.[36] The exceptions to this rule are patients with rapidly progressive or extensive visceral disease in whom a rapid response is needed or patients with oligometastases treated with multimodality strategies with curative intent.

Following the introduction of the taxanes, other cytotoxic agents were developed: vinorelbine[37] and other vinca alkaloids, gemcitabine,[38] capecitabine,[39] ixabepilone,[40] and eribulin.[41] These agents have been incorporated into the management of metastatic breast cancer, with capecitabine playing a particularly major role on the basis of its excellent therapeutic index once the appropriate dose for each patient is determined. Clinical trials of combination and sequential therapy continued and informed the development of third-generation adjuvant chemotherapy trials.

Much of the progress in breast cancer was the result of the development of adjuvant chemotherapy. Fisher and Bonadonna showed in the mid-1970s that the addition of adjuvant chemotherapy to definitive surgery improved disease-free and overall survival in primary breast cancer.[41a,41b] The results of these seminal trials were presented at the respective annual meetings of ASCO. Subsequently, multiple confirmatory trials were summarized by the Early Breast Cancer Trialists Collaborative Group.[41c] Additional publications from this group demonstrated that in the adjuvant setting, combination chemotherapy was superior to single-agent chemotherapy; that anthracycline-based regimens were superior to nonanthracycline-based regimens; and that about 6 months of chemotherapy were sufficient, with longer treatments not resulting in additional benefit.[41d,41e] Clinical trials and the meta-analysis also showed the incremental benefit of combining chemotherapy and endocrine therapy in sequential schedules for women with hormone receptor–positive breast cancer. Another major step forward came with the introduction of taxanes into adjuvant therapy.[41f,41g] In 1992, the efficacy of adjuvant chemotherapy and endocrine therapy was established in lymph node–negative breast cancer, and exploratory analyses indicated that such treatments had a positive therapeutic ratio in older patients with breast cancer.[41h] Randomized trials provided evidence for the incremental benefit of dose-dense administration of chemotherapy.[41i] Additional trials and the meta-analysis demonstrated no significant benefit from the use of high-dose chemotherapy with hematopoietic stem cell rescue for breast cancer.[41j] Such incremental progress now provides a greater than 50% reduction in the odds of recurrence and a similar reduction in odds of death for patients with primary breast cancer.

With the completion of the Human Genome Project, gene expression technology led to the identification of various molecular subtypes of breast cancer, subtypes that today are considered separate entities, with different clinical courses, patterns of metastases, and sensitivity to existing therapeutic agents.[42] Although gene expression technology has become much less expensive, the great majority of patients have no easy access to such assays. Thus, the genomic classification has been superseded by a clinical-pathological classification on the basis of expression of estrogen receptor, progesterone receptor, HER2, and Ki-67 of grade.[43,44] It should be understood that the two classifications differ, and the overlap between similar subtypes is only approximately 75%. However, this represents a practical compromise.

Gene expression profiling identified the basal-like subtype as being arguably one of the most aggressive types of breast cancer, with a higher probability of metastasis and death from progressive disease.[45] In clinical practice, the term triple-negative breast cancer, indicating the absence of expression of estrogen receptor (ER) and progesterone receptor (PR) and normal expression of HER, has acted as a ready clinical surrogate for the basal-like subtype.[45,46] Although responsive to chemotherapy, many responses in the metastatic setting

are short, with median overall survival remaining less than 2 years. Although standard chemotherapy includes all the agents listed earlier, there is increasing interest in incorporating platinum salts into systemic regimens.[47] Triple-negative breast cancer also includes most of the *BRCA1* mutated tumors, which appear quite responsive to PARP inhibitors,[48] so there is much interest in pivotal trials of these agents. Several signaling pathways are under intense scrutiny, and signaling inhibitors alone or in combination are being tested.

ER: The First Targeted Therapy

The development of therapeutics for ER-expressing breast cancers has been one of the great clinical advances of the past 50 years and has served as a paradigm for the development of targeted therapies in oncology. It had been known for more than a century that hormonal ablation of ovarian, pituitary, or adrenal function could cause tumor responses among some patients with advanced breast cancer. In the late 1960s and early 1970s, tumor expression of steroid hormone receptors (ER and PR) was identified as both a critical prognostic marker and the seminal biomarker predicting benefit from anti-estrogen treatments.[49] Randomized clinical trials subsequently proved that, across the full spectrum of breast disease ranging from cancer prevention[50] to management of ductal carcinoma in situ[22] to treatment of early[51] and advanced stage breast cancer, anti-estrogen therapies have powerful impact on the natural history of ER-expressing breast cancers, and that ER expression is the sine qua non for clinical benefit. ER expression correlates closely with other important clinical and pathological features of breast cancer, including tumor grade, HER2 expression, recurrence risk, and benefit from adjuvant chemotherapy,[52] and helps define the clinically important subtypes of breast cancers. Recognition of the relationship between tumor ER expression and clinical outcomes served as the model for biomarker/targeted-agent clinical translational research, heralding a new era for detailed clinicopathological correlations and subset analyses now found widely throughout oncology.

Presently, anti-estrogen therapies are a mainstay of treatment of ER-positive breast cancers. As most breast cancers are ER positive, and given the worldwide prevalence of the disease, it is arguable that anti-estrogen treatments have had greater global impact that any other treatment intervention in cancer medicine. The innumerable randomized trials of adjuvant endocrine therapy engendered innovative biostatistical meta-analyses and investigator collaborations, now the norm in international oncology, and helped establish the paradigm of adjuvant drug treatment for solid tumors. Five years of therapy with the selective estrogen receptor modulator tamoxifen or aromatase inhibitors (AIs, which cause estrogen depletion) reduces breast cancer recurrence and improves overall survival in women with ER-positive early-stage breast cancer and has been the worldwide standard of care.[1]

Despite adjuvant therapy with 5 years of endocrine agents, there remains persistent risk of tumor recurrence beyond 5 years of treatment. Recent data suggest that longer durations of adjuvant endocrine therapy—out to 10 years—lower the risk of tumor recurrence and improve survival[53] These findings underscore the chronic nature of ER-positive breast cancer, and the innovation of long durations of therapy to prevent late recurrence is the new frontier in adjuvant endocrine treatment. Additional studies are needed to clarify which tumors pose persistent jeopardy for recurrence.

The importance of endocrine agents for breast cancer, as well as an appreciation for their adverse effects and the growing use of long durations of treatment have spawned new areas of oncology research in survivorship, symptom control, and compliance with medical therapy. In one of the first commercial applications of genomic science, gene expression assays centered on ER expression identify which patients with ER-positive breast cancers warrant chemotherapy in addition to endocrine therapy and which can be treated adequately with endocrine therapy alone.[54]

Resistance to endocrine therapies remains a clinical and scientific challenge. Loss of ER expression does not account for most instances of tumor resistance. Ongoing efforts to enhance outcomes in ER-positive breast cancer focus on targeting pathways linked to ER function, such as the PIK3CA/mTOR and cyclin pathways, which are frequently mutated in ER-positive cancers,[54] characterization of acquired ER mutations, and identifying subsets of subsets of tumors with specific biologic features and clinical needs. Genomic breast cancer sequencing will, we hope, identify new therapeutic targets for use alongside hormonal therapies for ER-positive breast cancers.[54]

Breast Cancer Prevention

Although the major focus of ER-targeted therapy has been the treatment of existing breast cancer, whether in the adjuvant or metastatic setting, the application of ER-targeted therapy to preventing breast cancer has represented an important recent advance. Large, multinational chemoprevention trials involving tens of thousands of women have provided level 1 evidence of benefit (and US Food and Drug Administration approval) of two SERMS (tamoxifen and raloxifene) and emerging evidence of benefit of two AIs.

Four randomized trials conducted in North America and Europe,[50,55-57] involving almost 23,000 pre- and postmenopausal women, have identified beneficial preventive effects of tamoxifen (versus placebo) administered for 5 to 8 years (Table 1). Tamoxifen has been shown to lower breast cancer risk by about one-third, with evidence of enduring risk reduction out to at least 10 years.[57] Effects on invasive and noninvasive breast cancer are similar; however, benefits are seen only for ER-positive breast cancer risk, which is reduced by almost 50%. Although the relative risk reduction is large, absolute benefits are small (2% to 4% in the populations studied) and these benefits are accompanied by an increased risk of endometrial cancer, thromboembolic events, cataracts, and hot flashes. Thus, the net benefit is small in all but the highest risk women. This, in turn, has resulted in a reluctance of many physicians to prescribe tamoxifen to most women who could potentially benefit and reluctance by many women to accept it as a risk-reducing therapy.

The Study of Tamoxifen and Raloxifene trial in postmenopausal women, which compared tamoxifen to raloxifene (an agent targeting ER that was initially developed to increase bone density and had not been associated with an increased risk of endometrial cancer), was conducted in an attempt to find an agent with a better risk-benefit profile than tamoxifen. In the short term (about 4 years),[58] the risk of invasive breast cancer was similar with both drugs; however, raloxifene was less effective in reducing noninvasive breast cancer risk. With longer follow-up (10 years), raloxifene was less effective than tamoxifen (25% higher risk of invasive breast cancer).[59] As a result, despite a

Table 1. Randomized Breast Cancer Prevention Trials of Hormonal Interventions

Trial and Year	Comparison	Eligibility Criteria	No. Randomly Assigned	Effect on Breast Cancer
NSABP-P1,[50] 1998	Tamoxifen 20 mg per day *v* placebo for 5 years	Gail 5-year risk score > 1.66%	13,388	Reduced invasive, noninvasive breast cancer (HR, 0.51) Effect on ER+ but not ER− cancers
IBIS-I,[55] 2007	Tamoxifen 20 mg per day *v* placebo for 5 years	Relative risk ≥ 2 × general population (on basis of family history, results of previous benign breast biopsies)	7,139	Reduced invasive, noninvasive breast cancer (HR, 0.73; 95% CI, 0.58 to 0.91) Effect on ER+ but not ER− cancers
Marsden,[56] 2007	Tamoxifen 20 mg per day *v* placebo for 8 years	Family history of breast cancer	2,471	Nonsignificantly lower invasive breast cancer (HR, 0.78; 95% CI, 0.58 to 1.04) Effect on ER+ but not ER− cancers
Veronesi et al,[57] 2007	Tamoxifen 20 mg per day *v* placebo for 5 years	Average breast cancer risk, prior hysterectomy	5,408	Nonsignificantly lower invasive, noninvasive breast cancer (HR, 0.84; 95% CI, 0.60 to 1.17) Significantly reduced breast cancer in high-risk women (HR, 0.24; 95% CI, 0.10 to 0.59) Significantly reduced breast cancer in women receiving estrogen replacement (HR, 0.43; 95% CI, 0.20 to 0.95)
NSABP (STAR),[58,59] 2006, 2010	Raloxifene 60 mg per day *v* tamoxifen 20 mg per day for 5 years	Gail 5-year risk score > 1.6% (postmenopausal)	19,747	Comparable invasive breast cancer risk at 47 months (HR, 1.03; 95% CI, 0.82 to 1.28) Increased invasive breast cancer risk with raloxifene at 81 months (HR, 1.24; 95% CI, 1.05 to 1.47) More noninvasive breast cancers with raloxifene
MAP.3,[60] 2011	Exemestane 25 mg per day *v* placebo for 5 years (analysis at 35 months median follow-up)	Gail 5-year risk score > 1.66% (postmenopausal)	4,560	Reduced invasive breast cancer (HR, 0.35; 95% CI, 0.18 to 0.70) Reduced invasive and noninvasive breast cancer (HR, 0.47; 95% CI, 0.27 to 0.79) Reduced ER+ but not ER− cancers
IBIS-II,[61] 2013	Anastrozole 1 mg per day *v* placebo for 5 years	Relative risk ≥ 2 × general population (family history, benign breast disease; postmenopausal)	3,864	Reduced invasive, noninvasive breast cancer (HR, 0.47; 95% CI, 0.32 to 0.68) Reduced ER+ but not ER− cancers

Abbreviations: ER, estrogen receptor; HR, hazard ratio; IBIS-I, International Breast Cancer Intervention Study I; IBIS-II, International Breast Cancer Intervention Study II; MAP.3, Mammary Prevention 3; NSABP-P1, National Surgical Adjuvant Breast and Bowel Project trial P1; STAR, Study of Tamoxifen and Raloxifene.

more favorable adverse effect profile of raloxifene (lower risk of endometrial cancer, cataracts, and thromboembolic events), this agent has not been widely embraced as a substitute for tamoxifen in breast cancer prevention.

Two recent trials compared the preventive effects of an AI (exemestane, anastrozole) versus placebo (Table 1).[60,61] Both identified a marked reduction in invasive breast cancer risk of about one half to two thirds. Toxicities were lower than expected from the use of these agents in the adjuvant setting, with no evidence of increased fracture risk and minimal impact on quality of life. Both trials used placebo (rather than tamoxifen) in their comparison arm; as a result, it is difficult to ascertain the relative benefits of these agents versus tamoxifen. However, the favorable adverse effect profile of AIs that has been reported in the prevention setting may lead to greater use of these agents.

Tamoxifen is the only agent with demonstrated preventive efficacy in premenopausal women. In postmenopausal women, raloxifene and the AIs are potential options. Individual patient characteristics (including prior hysterectomy) and preferences should guide agent selection in postmenopausal women; modeling benefits and harms may facilitate this selection.[62]

Unfortunately, no survival benefits have been identified in any of these prevention trials; short follow-up and early stopping (with unblinding and cross-over of control subjects to the active agent) have made it difficult to identify any survival benefits that may exist. None of these endocrine agents has lowered risk of ER-negative breast cancer. These factors, and the potential for serious toxicities, have also contributed to the continued low uptake of these agents.

Prophylactic mastectomy has also been investigated as a means of lowering breast cancer risk. It has been associated with lower breast cancer incidence in selected high or higher risk populations,[63] and its use may be associated with reduced breast cancer mortality in BRCA mutation carriers. However, it can adversely affect body image and quality of life, even when combined with reconstruction. There is growing acceptance of its role in selected high-risk women, notably BRCA mutation carriers.

Lifestyle change (physical activity,[64] avoidance of postmenopausal obesity,[65] dietary change, vitamin supplementation) has also been advocated as a means of preventing breast cancer, based largely on associations of these factors with lower risk. The feasibility of long-term lifestyle change is controversial, but modest change is likely feasible in motivated women. A Women's Health Initiative randomized trial of dietary fat reduction identified a small (9%) reduction in breast cancer risk that was of borderline statistical significance; a greater benefit was seen in more adherent women.[66] Randomized trials of vitamin D supplementation identified no evidence of reduction in breast cancer incidence.

An effective and broadly accepted approach to breast cancer prevention remains elusive. Healthy women have less tolerance for toxicity, particularly serious events such as cancer and thromboembolism. The continuing challenge will be to find approaches that are effective and have an acceptable risk-benefit ratio.

HER2-Positive Disease

In the late 1980s, *HER2* gene amplification was recognized as a prognostic marker for poor clinical outcome in early-stage breast cancer.[67,68] While retrospective studies suggested a preferential benefit with adjuvant anthracycline regimens,[69] the true revolution in therapy for HER2-positive patients awaited the development of the targeted monoclonal anti-HER2 antibody trastuzumab. In 1998, a randomized clinical trial showed an unprecedented improvement in survival when trastuzumab was added to standard chemotherapy in metastatic disease,[70] and by 2005, the use of adjuvant trastuzumab transformed the face of HER2-positive disease, substantially improving disease-free and overall survival.[13,71-73]

Trastuzumab resistance occurs in both the metastatic and adjuvant settings. Starting in 2007, several new drugs became available, including the small molecule tyrosine kinase inhibitor lapatinib, the anti HER2-HER3 dimerization antibody pertuzumab, and the antibody drug conjugate ado-trastuzumab emtansine or T-DM1 in 2013. These approvals were based on improvement in survival outcomes in metastatic patients with mostly trastuzumab-naive (pertuzumab[74]) or trastuzumab-exposed (lapatinib[18] and T-DM1[75]) breast cancer, and all these agents are now being tested in ongoing adjuvant trials. In 2014, the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial will be the first trial to report on whether dual anti-HER2 therapy with trastuzumab and lapatinib (in sequence or in combination) improves outcomes compared to single agent trastuzumab. The Addition to Chemotherapy and Herceptin (Trastuzumab) As Adjuvant Therapy in Patients With HER2-Positive Primary Breast Cancer (APHINITY) trial is testing the addition of pertuzumab to standard nonanthracycline or anthracycline-based chemotherapy plus trastuzumab. In addition, A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy (KATHERINE) is examining the role of postoperative T-DM1 versus trastuzumab in patients with HER2-positive disease and less than a pathologic complete response after preoperative therapy with a trastuzumab-based regimen.

The remarkable switch from a prognostic marker for worse survival in the absence of treatment to a predictive marker for improved outcome cemented the clinical utility of HER2 overexpression. HER2 amplification occurs in approximately 15% of all newly diagnosed patients.[76] Findings from the first generation of adjuvant HER2-targeted trials also led the American Society of Clinical Oncology and the College of American Pathologists to provide guidance on HER2 testing.[77] Earlier concerns about the high frequency of false-positive HER2 test results have diminished as a result of greater standardization of tissue handling, improved laboratory performance of HER2 testing, and more careful reporting of test results. Current guidelines examine less common clinical scenarios and expand the focus beyond specificity (false-positive results) to also address concerns about sensitivity (false-negative results).[77]

NSABP B-47 is now attempting to confirm retrospective, hypothesis-generating exploratory data from two of the adjuvant trastuzumab trials regarding a possible benefit in patients confirmed on central testing to have HER2-negative disease but whose tumors had initially tested positive in a local laboratory.[78,79] HER2-targeted therapy combined with radiation therapy is also the subject of another prospective trial in women with in situ disease (NSABP B43). In the meantime, prospective trials have shown no benefit from lapatinib[78] or pertuzumab[80] in HER2-negative metastatic disease.

Although few patients with node-negative disease and almost no patients with tumors measuring 1 cm or less were eligible for the first generation of adjuvant trials, retrospective institutional series suggest that patients with small node-negative, HER2-positive tumors have a high enough risk of recurrence in the absence of therapy to potentially support the use of adjuvant trastuzumab.[78,81,82] Smaller tumor size retains prognostic utility in small untreated HER2-positive tumors, and the first results from a single-arm study of 12 weeks of paclitaxel/trastuzumab followed by trastuzumab were recently reported with a short median follow-up),[82a] with the suggestion that such therapy resulted in an exceptionally low relapse rate. A subsequent study (ATEMPT) will soon test this regimen against T-DM1 in a similar patient group.

The clinical landscape for HER2-positive breast cancer was forever altered with the approval of trastuzumab in 1998. Many, though not all, HER2-positive patients with metastatic disease face a manageable chronic disease. The development of metastases in sanctuary sites like the CNS has been seen more commonly as systemic therapy has improved.

Questions remain about optimal sequence, duration, and combination of various anti-HER2 targeted agents, with and without chemotherapy. Our understanding regarding mechanisms of resistance to HER2-targeted therapy (including perturbations of the PI3 kinase pathway) is still limited, and clinical applications that exploit interactions with this and other growth factor pathways are still early in development.[83] Despite the enormous accomplishments of the past 25 years, much remains to be learned about the optimal clinical management of HER2-positive breast cancer.

The past 50 years transformed the care of patients with breast cancer, reducing morbidity and mortality through the application of basic scientific principles to the clinic. Although enormous progress has been made, many important challenges remain. To name but a few of these: though effective prevention approaches exist, they have had little effect as a result of poor uptake in the general medical community; improved breast imaging has revealed the existence of large populations that may never require treatment, yet we have no effective means of separating the dangerous from the innocuous; the majority of women relapsing and dying of ER-positive breast cancer do so as a result of dormant micrometastases, which are largely untouched by initial adjuvant systemic therapies; resistance to all systemic therapies remains a major problem; triple-negative breast cancer, dominated by genomic chaos, does not seem likely to be amenable to the targeted therapies that have transformed ER- and HER2-positive breast cancer; and the success of systemic therapies for HER2-positive disease has resulted in a progressive increase in symptomatic CNS relapses, uncontrolled by standard monoclonal antibody therapies.

Other challenges exist, challenges deriving from the real successes of recent years. The development of deep genomic sequencing has revealed a veritable forest of orphan diseases, rendering the classic phase III trial (the engine of clinical success for decades) virtually impossible going forward for the many biologic subsets we face. We will need new approaches both to the biology of the disease, as well as to the clinical trials we use to apply that biology. We will need different regulatory approaches, renewed and transformed cooperative groups, improved collaboration at an international level, and recognition that

therapy, to be effective, must be accessible to all who suffer from the disease.

These are important challenges. But as the American Society of Clinical Oncology faces its second half-century, there is no question but that our community, the front-line of clinical research and practice, is up for the challenge.

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REFERENCES

1. NIH Consensus Development Conference on the Treatment of Early-Stage Breast Cancer. Bethesda, Maryland, June 18-21, 1990. J Natl Cancer Inst Monogr 1-187, 1992

2. Tuttle TM, Jarosek S, Habermann EB, et al: Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. J Clin Oncol 27:1362-1367, 2009

3. Carpin LB, Bickford LR, Agollah G, et al: Immunoconjugated gold nanoshell-mediated photothermal ablation of trastuzumab-resistant breast cancer cells. Breast Cancer Res Treat 125:27-34, 2011

4. Wapnir IL, Anderson SJ, Mamounas EP, et al: Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 24:2028-2037, 2006

5. Fisher B, Anderson S, Fisher ER, et al: Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet 338:327-331, 1991

6. Anderson SJ, Wapnir I, Dignam JJ, et al: Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. J Clin Oncol 27:2466-2473, 2009

7. Mamounas EP: Ipsilateral breast tumor recurrence after lumpectomy: Is it time to take the bull by the horns? J Clin Oncol 19:3798-3800, 2001

8. Aebi S, Gelber S, Lang I, et al: Chemotherapy prolongs survival for isolated local or regional recurrence of breast cancer: The CALOR trial (Chemotherapy as Adjuvant for Locally Recurrent breast cancer; IBCSG 27-02, NSABP B-37, BIG 1-02). Cancer Res 72:96s, 2012 (abstr S3-2)

9. Krag DN, Weaver DL, Alex JC, et al: Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 2:335-339, 1993

10. Krag D, Weaver D, Ashikaga T, et al: The sentinel node in breast cancer—a multicenter validation study. N Engl J Med 339:941-946, 1998

11. Giuliano AE, Kirgan DM, Guenther JM, et al: Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 220:391-398, 1994

12. Giuliano AE, Hunt KK, Ballman KV, et al: Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. JAMA 305:569-575

13. Galimberti V, Cole BF, Zurrida S, et al: Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): A phase III randomised controlled trial. Lancet Oncology 14:297-305, 2013

14. Fisher B, Mamounas EP: Preoperative chemotherapy: A model for studying the biology and therapy of primary breast cancer. J Clin Oncol 13:537-540, 1995

15. Fisher B, Brown A, Mamounas E, et al: Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 15:2483-2493, 1997

16. Fisher B, Bryant J, Wolmark N, et al: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 16:2672-2685, 1998

17. Bear HD, Anderson S, Brown A, et al: The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 21:4165-4174, 2003

18. Bear HD, Anderson S, Smith RE, et al: Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 24:2019-2027, 2006

19. Bonadonna G, Veronesi U, Brambilla C, et al: Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst 82:1539-1545, 1990

20. Millar EK, Graham PH, O'Toole SA, et al: Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-biomarker panel. J Clin Oncol 27:4701-4708, 2009

21. Cheng SH, Horng CF, West M, et al: Genomic prediction of locoregional recurrence after mastectomy in breast cancer. J Clin Oncol 24:4594-4602, 2006

22. Allred DC, Anderson SJ, Paik S, et al: Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: A study based on NSABP protocol B-24. J Clin Oncol 30:1268-1273, 2012

23. Voduc KD, Cheang MC, Tyldesley S, et al: Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 28:1684-1691

24. Nguyen PL, Taghian AG, Katz MS, et al: Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol 26:2373-2378, 2008

25. Kyndi M, Sorensen FB, Knudsen H, et al: Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: The Danish Breast Cancer Cooperative Group. J Clin Oncol 26:1419-1426, 2008

26. Greenspan EM, Fieber M, Lesnick G, et al: Response of advanced breast carcinoma to the combination of the antimetabolite, methotrexate, and the alkylating agent, thio-TEPA. J Mt Sinai Hosp 30:246-267, 1963

27. Cooper RG: Combination chemotherapy of breast cancer. Mt Sinai J Med 52:443-446, 1985

28. Middleman E, Luce J, Frei E 3rd: Clinical trials with adriamycin. Cancer 28:844-850, 1971

29. Smalley RV, Carpenter J, Bartolucci A, et al: A comparison of cyclophosphamide, adriamycin, 5-fluorouracil (CAF) and cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone (CMFVP) in patients with metastatic breast cancer: A Southeastern Cancer Study Group project. Cancer 40:625-632, 1977

30. Sledge GW, Jr., Loehrer PJ, Sr., Roth BJ, et al: Cisplatin as first-line therapy for metastatic breast cancer. J Clin Oncol 6:1811-1814, 1988

31. Kolaric K RA: Phase II clinical trial of cis-dichlorodiammine platinum (cis-DDP) for antitumorigenic activity in previously untreated patients with metastatic breast cancer. Cancer Chemother Pharmacol 11:108-112, 1983

32. Ghersi D, Wilcken N, Simes J, et al: Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev 2:CD003366, 2005

33. Fossati R, Confalonieri C, Torri V, et al: Cytotoxic and hormonal treatment for metastatic breast cancer: A systematic review of published randomized trials involving 31,510 women. J Clin Oncol 16:3439-3460, 1998

34. Norton L, Simon R: The Norton-Simon hypothesis revisited. Cancer Treat Rep 70:163-169, 1986

35. Sledge GW, Neuberg D, Bernardo P, et al: Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An intergroup trial (E1193). J Clin Oncol 21:588-592, 2003

36. Cardoso F, Harbeck N, Fallowfield L, et al: Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 23:vii11-vii19, 2012 (suppl 7)

37. Gregory RK, Smith IE: Vinorelbine—a clinical review. Br J Cancer 82:1907-1913, 2000

38. Takeda AL, Jones J, Loveman E, et al: The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: A systematic review and economic evaluation. Health Technol Assess 11:1-62, 2007

39. O'Shaughnessy JA, Kaufmann M, Siedentopf F, et al: Capecitabine monotherapy: Review of studies in first-line HER-2-negative metastatic breast cancer. Oncologist 17:476-484, 2012

40. Yardley DA: Activity of ixabepilone in patients with metastatic breast cancer with primary resistance to taxanes. Clin Breast Cancer 8:487-492, 2008

41. Pean E, Klaar S, Berglund EG, et al: The European Medicines Agency review of eribulin for the treatment of patients with locally advanced or metastatic breast cancer: Summary of the scientific assessment of the committee for medicinal products for human use. Clin Cancer Res 18:4491-4497, 2012

41a. Fisher B, Carbone P, Economou SG, et al: 1-Phenylalanine mustard (L-PAM) in the management of primary breast cancer: A report of early findings. N Engl J Med 292:117-122, 1975

41b. Bonadonna G, Brusamolino E, Valagussa P, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-410, 1976

41c. Early Breast Cancer Trialists' Collaborative Group: Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: An overview of 61 randomized trials among 28,896 women—Early Breast Cancer Trialists' Collaborative Group. N Engl J Med 319:1681-1692, 1988

41d. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women—Early Breast Cancer Trialists' Collaborative Group. Lancet 339:71-85, 1992

41e. Early Breast Cancer Trialists' Collaborative Group: Polychemotherapy for early breast cancer: An overview of the randomised trials—Early Breast Cancer Trialists' Collaborative Group. Lancet 352:930-942, 1998

41f. Henderson IC, Berry DA, Demetri GD, et al: Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 21:976-983, 2003

41g. Mackey JR1, Martin M, Pienkowski T, et al: Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial. Lancet Oncol 14:72-80, 2013

41h. Muss HB, Woolf S, Berry D, et al: Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA 293:1073-1081, 2005

41i. Citron ML, Berry DA, Cirrincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431-1439, 2003

41j. Berry DA, Ueno NT, Johnson MM, et al: High-dose chemotherapy with autologous stem-cell support as adjuvant therapy in breast cancer: Overview of 15 randomized trials. J Clin Oncol 29:3214-3223, 2011

42. Perou CM, Sorlie T, Eisen MB, et al: Molecular portraits of human breast tumours. Nature 406:747-752, 2000

43. Tang PSK, Hicks DG: Molecular classification of breast carcinomas by immunohistochemical analysis: Are we ready? Diagn Mol Pathol 18:125-132, 2009

44. Fumagalli D, Andre F, Piccart-Gebhart MJ, et al: Molecular biology in breast cancer: Should molecular classifiers be assessed by conventional tools or by gene expression arrays? Crit Rev Oncol Hematol 84:e58–e69, 2012 (suppl 1)

45. Prat A, Adamo B, Cheang MC, et al: Molecular characterization of basal-like and non-basal-like triple-negative breast cancer. Oncologist 18:123-133, 2013

46. Lehmann BD, Bauer JA, Chen X, et al: Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 121:2750-2767, 2011

47. Liu M, Mo QG, Wei CY, et al: Platinum-based chemotherapy in triple-negative breast cancer: A meta-analysis. Oncol Lett 5:983-991, 2013

48. Underhill C, Toulmonde M, Bonnefoi H: A review of PARP inhibitors: From bench to bedside. Ann Oncol 22:268-279, 2011

49. Schiff R, Osborne CK, Fuqua SAW: Clinical aspects of estrogen and progesterone receptors, in Harris JR, Lippman ME, Osborne CK, et al (eds): Diseases of the Breast (ed 4). Philadelphia, PA, Lippincott, Williams, and Wilkins, 2009

50. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90:1371-1388, 1998

51. Early Breast Cancer Trialists' Collaborative Group: Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. Lancet 378:771-784, 2011

52. Paik S, Tang G, Shak S, et al: Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 24:3726-3734, 2006

53. Davies C, Pan H, Godwin J, et al: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 381:805-816, 2013

54. Cancer Genome Atlas Network: Comprehensive molecular portraits of human breast tumours. Nature 490:61-70, 2012

55. Cuzick J, Forbes JF, Sestak I, et al: Long-term results of tamoxifen prophylaxis for breast cancer: 96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 99:272-282, 2007

56. Powles TJ, Ashley S, Tidy A, et al: Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 99:283-290, 2007

57. Veronesi U, Maisonneuve P, Rotmensz N, et al: Tamoxifen for the prevention of breast cancer: Late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst 99:727-737, 2007

58. Vogel VG, Costantino JP, Wickerham DL, et al: Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 295:2727-2741, 2006

59. Vogel VG, Costantino JP, Wickerham DL, et al: Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila) 3:696-706, 2010

60. Goss PE, Ingle JN, Ales-Martinez JE, et al: Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 364:2381-2391, 2011

61. Cuzick J, Sestak I, Forbes JF, et al: Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): An international, double-blind, randomised placebo-controlled trial. Lancet, 2013

62. Freedman AN, Yu B, Gail MH, et al: Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. J Clin Oncol 29:2327-2333, 2011

63. Lostumbo L, Carbine NE, Wallace J: Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev 11:CD002748, 2010

64. Friedenreich CM, Neilson HK, Lynch BM: State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer 46:2593-2604, 2010

65. Cleary MP, Grossmann ME, Ray A: Effect of obesity on breast cancer development. Vet Pathol 47:202-213, 2010

66. Prentice RL, Caan B, Chlebowski RT, et al: Low-fat dietary pattern and risk of invasive breast cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 295:629-642, 2006

67. Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177-182, 1987

68. Slamon DJ, Godolphin W, Jones LA, et al: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 244:707-712, 1989

69. Muss HB, Thor AD, Berry DA, et al: C-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med 330:1260-1266, 1994

70. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-792, 2001

71. Joensuu H, Bono P, Kataja V, et al: Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: Final results of the FinHer Trial. J Clin Oncol 27:5685-5692, 2009

72. Perez EA, Romond EH, Suman VJ, et al: Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: Joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 29:3366-3373, 2011

73. Slamon D, Eiermann W, Robert N, et al: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273-1283, 2011

74. Baselga J, Cortes J, Kim SB, et al: Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366:109-119, 2012

75. Verma S, Miles D, Gianni L, et al: Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367:1783-1791, 2012

76. Hammond ME, Hayes DF, Dowsett M, et al: American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28:2784-2795, 2010

77. Khatcheressian JL, Hurley P, Bantug E, et al: Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 31:961-965, 2013

78. Aaltonen T, Abulencia A, Adelman J, et al: Observation of orbitally excited B(s) mesons. Phys Rev Lett 100:082001, 2008

79. Bardhan R, Chen W, Bartels M, et al: Tracking of multimodal therapeutic nanocomplexes targeting breast cancer in vivo. Nano Lett 10:4920-4928, 2010

80. Gianni L, Llado A, Bianchi G, et al: Open-label, phase II, multicenter, randomized study of the efficacy and safety of two dose levels of pertuzumab, a human epidermal growth factor receptor 2 dimerization inhibitor, in patients with human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 28:1131-1137, 2010

81. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al: High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol 27:5700-5706, 2009

82. Curigliano G, Viale G, Bagnardi V, et al: Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol 27:5693-5699, 2009

82a. Tolaney SM, Barry WT, Dang CT et al: A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). San Antonio Breast Cancer Symposium, December 10-14, 2013 (abstr SI-04)

83. Lauring J, Park BH, Wolff AC: The phosphoinositide-3-kinase-Akt-mTOR pathway as a therapeutic target in breast cancer. J Natl Compr Canc Netw 11:670-678, 2013

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