Over the past 20 years we have witnessed the emergence of a new generation of aromatase inhibitors as valuable antiestrogens in the management of both advanced and early-stage breast cancer. In addition, the list of cytotoxic chemotherapeutic agents useful in the control of breast cancer has grown considerably. The emergence of anthracyclines was a major chemotherapeutic step forward in the 1980s, and the taxanes have clearly been the agents with the greatest impact on breast cancer treatment over the past decade. The end of the past 2 decades has been characterized by a greater understanding of the molecular biology of breast cancer, rational drug design, and the development of agents that disrupt specific cellular targets and pathways. The development of better prognostic and predictive assays that employ a panel of genes involved in the malignant and metastatic phenotype promises to allow clinicians to better select patients who could forgo adjuvant chemotherapy. Finally, adjunctive and supportive therapy of breast cancer has evolved substantially over the past 20 years. This review will highlight some of the landmark accomplishments during this time, and offer a glimpse at where we might be 20 years from now.

The first observations of hormone-dependency of breast cancer were made over a century ago, when ovarian ablation was observed to cause regression of systemic disease.[1] The past 2 decades have witnessed the emergence of a new generation of aromatase inhibitors as valuable antiestrogens in the management of both advanced and early-stage breast cancer. The role of ovarian function suppression in the adjuvant treatment of premenopausal women with hormone-sensitive breast cancer is only now being prospectively investigated in randomized trials, after Beatson’s early observation. Progress in the development of effective nonantiestrogen therapy (eg, cytotoxics and targeted agents) for breast cancer has been indeed much more contemporary. The past 2 decades constitutes about one-half of what most would consider to represent the “chemotherapy era.”

The list of cytotoxic chemotherapeutic agents useful in the control and cure of breast cancer is long, and growing (Table 1). A high level of evidence-based medicine supports the use of sequential single-agent chemotherapy for metastatic disease, with judicious use of combination chemotherapy arguably indicated for selected patients.[2] Just as the emergence of anthracyclines was a major chemotherapeutic step forward in the 1980s, the taxanes have clearly been the agents with the greatest impact on breast cancer treatment over the past decade. Dose escalation of cytotoxic chemotherapeutic agents into the realm of myelosuppression requiring autologous bone marrow and peripheral blood stem cell support did not improve survival for patients with either metastatic or early-stage disease[3-5]—this was a lesson learned the hard way. More modest dose escalation of agents such as paclitaxel and docetaxel (Taxotere) has not prolonged time to disease progression.[6,7] More frequent dosing of paclitaxel has proven superior to standard every-3-week dosing,[8] and indeed dose-dense chemotherapy with anthracycline and taxane improves disease-free and overall survival as compared to conventional every-3-week dosing.[9]

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The end of the past 2 decades has been characterized by a greater understanding of the molecular biology of breast cancer, rational drug design, and the development of agents that perturb specific, often premeditated cellular targets and pathways. The emergence of trastuzumab (Herceptin)\(^{[10-12]}\) and, in the near future, lapatinib (Tykerb),\(^{[13,14]}\) agents that improve outcomes for patients with HER2-overexpressing breast cancers, is one obvious example. The benefit observed for the addition of the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (Avastin) to weekly paclitaxel in metastatic breast cancer as reported in Eastern Cooperative Oncology Group (ECOG) 2100 represents another.\(^{[15]}\) Whether the target is angiogenesis, HER-family signaling, apoptosis, or other pathways, numerous agents in development are likely to emerge from ongoing clinical trials, and optimizing their use in combinations with both cytotoxics and other targeted agents will remain a challenge as we begin to morph beyond the chemotherapy era.

It is well recognized that in the effort to cure early-stage breast cancer, many women will receive adjuvant chemotherapy without deriving benefit. The development of better prognostic and predictive assays that employ a panel of genes involved in the malignant and metastatic phenotype promises to allow clinicians to better select those patients who cold forego adjuvant chemotherapy.\(^{[16-19]}\) One such assay, the Oncotype DX 21-gene reverse transcriptase polymerase chain reaction assay is already used in the clinic and is being further studied in a randomized phase III trial.\(^{[19,20]}\)

Finally, adjunctive and supportive therapy of breast cancer has evolved substantially over the past 20 years. The use of granulocyte colony-stimulating factor (G-CSF, Neupogen) has ameliorated neutropenic complications of chemotherapy (and facilitated dose-dense chemotherapy), erythropoietin has mitigated against anemia, and bisphosphonates have reduced skeletal complications. Newer generation antiemetics have lessened chemotherapy-induced nausea and vomiting. Ongoing trials are examining pharmacologic means of preventing peripheral neuropathy, mucositis, and cognitive dysfunction.

This review will highlight some of the landmark accomplishments of the past 20 years, and offer a glimpse at where we might be 20 years from now.

**Adjuvant Chemotherapy**
Over the past 2 decades, numerous clinical trials have established the benefit of anthracycline-based chemotherapy over non-anthracycline-containing chemotherapy, a finding that has been substantiated by a meta-analysis showing a decline in breast cancer mortality during that time (Figure 1).[21] More recent analysis of outcomes from several of these trials suggests that the differential benefit of anthracycline-containing chemotherapy may be confined to or largely derived in those patients with HER2-overexpressing tumors.[22,23] Current investigation focuses on whether amplification of the topoisomerase II-alpha gene may be a useful aid in predicting for greater anthracycline benefit.[24]

Numerous trials have demonstrated the benefit of the addition of paclitaxel and docetaxel in improving disease-free and overall survival in early breast cancer,[25-28] and these agents have become standard components in the adjuvant and neoadjuvant therapy of early-stage disease. The recently reported ECOG 1199 adjuvant trial showed no significant difference in efficacy between these two taxanes, with less toxicity noted for paclitaxel (Table 2).[29]

A recent report indicates the feasibility of integrating nanoparticle albumin-bound paclitaxel (Abraxane) into dose-dense adjuvant chemotherapy.[30] Ongoing Intergroup studies are comparing paclitaxel to doxorubicin-cyclophosphamide for lower-risk early-stage disease, and weekly to every-2-week paclitaxel. Examination of the potential contribution of agents not currently considered standard in the adjuvant setting, such as gemcitabine (Gemzar) and capecitabine (Xeloda), is also ongoing.
One of the most exciting developments of the past 2 decades has been the demonstration of improved disease-free and overall survival for the addition of the monoclonal antibody trastuzumab when added to chemotherapy for patients with HER2-positive, early-stage breast cancer.[31-34] The approximately 50% reduction in the annual odds of recurrence seen almost uniformly in five
adjuvant trials that have involved over 10,000 patients has established a role for trastuzumab in early-stage disease (Figure 2).\[4,31\] Clearly, the advantages observed have outweighed the small but real incidence of significant, often reversible cardiac dysfunction noted. The HERA trial will examine whether 2 years of trastuzumab is better than 1, and other studies will evaluate the possibility that shorter duration trastuzumab therapy may be as effective as longer, given the provocative benefit reported for a 9-week exposure to trastuzumab in the FinHer trial.\[33\] The APHRODITE study will examine a potential role for lapatinib in the management of HER2-positive, early-stage disease (Figure 3).

![Figure 2: HERA Trial Design](image)

Given the demonstration of improved progression-free survival for the addition of bevacizumab to weekly paclitaxel in the treatment of metastatic breast cancer, adjuvant pilot feasibility trials are already well underway in anticipation of a large adjuvant trial that will examine the potential of this antiangiogenic agent in the management of earlier-stage disease (Figure 4). Results of randomized phase III trials in metastatic disease may motivate similar study of other agents, such as sunitinib (Sutent), an oral anti-VEGF and multikinase inhibitor with established single-agent activity in anthracycline- and taxane-refractory metastatic breast cancer.\[35\]

![Figure 4: Bevacizumab Trial](image)

Adjuvant Antiestrogen Therapy
The past 2 decades have clarified the optimal duration of tamoxifen therapy in the pre-adjuvant
aromatase inhibitor (AI) era. Since then, numerous randomized trials, reviewed by Drs. Perez and Weilbaecher in their article on page 1029 of this issue, have established the role of the aromatase inhibitors anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) as valuable agents either instead of or sequentially with tamoxifen. The more widespread use of AIs has heightened awareness of the need to monitor bone density and employ strategies to mitigate against its loss (exercise, calcium, vitamin D, bisphosphonates). Fulvestrant (Faslodex), the parenteral selective estrogen receptor downregulator used in the management of metastatic disease, may ultimately find a role in earlier-stage breast cancer.

With respect to the timing of antiestrogen therapy, a large randomized trial has demonstrated that it is appropriate to delay initiation of tamoxifen until the completion of chemotherapy. [36] Similarly, in a sub-group analysis of the Intergroup 0102 trial, no adverse effect on local or systemic control was noted for concurrent use of tamoxifen and adjuvant radiotherapy, as compared with sequential administration. [37] Tamoxifen alone, without adjuvant radiotherapy, is a reasonable consideration for the older patient with a relatively small hormone-sensitive tumor, clear surgical margins, and negative axillary lymph nodes. [38]

Metastatic Disease

Breast cancer remains one of the most chemosensitive solid tumors (Table 1). Alkyting agents, antimetabolites, antitubulin agents, and others play an important role in controlling metastatic breast cancer. In the chemotherapeutic management of metastatic breast cancer, a recent e-mail survey of medical oncologists (n = 105) whose practices focus on this disease revealed that the median number of "lines" of chemotherapy employed in the management of this disease is 4, with a range of 1 to 10. [39] The notion that survival is a relevant endpoint for a clinical trial that simply examines, for example, first-line chemotherapy, would seem problematic given that the "story" of this disease process often unfolds like a book with many chapters. The notion that the specific strategy employed in Chapter 1 will ultimately dictate survival implies that subsequent lines of therapy have little or no potential impact on disease outcome. Indeed, trials that report survival advantages for combination chemotherapy over single-agent chemotherapy are often confounded by the lack of crossover from one single agent to the other. [2,40] The very notion itself is counterintuitive to many medical oncologists engaged in the treatment of women with this disease. One large trial that did plan a balanced crossover, ECOG 1193, showed no survival or quality-of-life advantage for combination anthracycline-taxane chemotherapy as compared the sequential use of the single agents. [41]

In the 1990s, there was a certain contagious optimism regarding the potential for high-dose chemotherapy sufficiently myelosuppressive as to require autologous hematocellular support, to prolong survival in advanced breast cancer. Unfortunately, the mature results of randomized trials did not bear out this promise. [3,4,42] At an auspicious moment in the 1990s when many medical oncologists felt empowered to offer high-dose chemotherapy regimens to patients outside the context of a clinical trial, and patients felt empowered to demand this as a standard option (with the inherent risks and toxicities), we learned that one of the most motivating trials, a presumably "positive" trial of high-dose chemotherapy from South Africa, [43] was fraudulent and falsified, a victim of scientific misconduct. [44] This unfortunate episode in breast cancer clinical trials has had major repercussions not only for breast cancer clinical research, but for all oncologic clinical research; the fallout has been more rigorous self-monitoring by clinical trialists of their own studies, and vigilant scrutiny by external monitors.

Key randomized phase III clinical trials have shown the potential benefits of specific combination chemotherapy regimens, such as docetaxel plus capecitabine [40] and paclitaxel plus gemcitabine. [45] For patients with HER2-positive breast cancers, the addition of trastuzumab to either paclitaxel [10] or docetaxel [11] significantly improved response rate, time to progression, and survival, and is now considered "standard of care" for patients with HER2-positive metastatic disease. While one randomized trial showed an advantage in time to progression for adding carboplatin to the paclitaxel plus trastuzumab doublet, [12] the recently reported Breast Cancer International Research Group (BCIRG) 007 trial did not demonstrate the same advantage when the taxane was docetaxel [45]; this would seem to both contradict promising preclinical data and perhaps dampen enthusiasm for a docetaxel/carboplatin/trastuzumab-only regimen in the adjuvant setting, as currently being studied in the BCIRG 006 trial. [46]

While most clinicians favor the continuation of trastuzumab beyond disease progression in the hope that it might augment the activity of yet another cytotoxic agent (eg, gemcitabine, vinorelbine, or capecitabine), no clinical trial data exist to address this practice. A recently reported randomized trial has demonstrated a doubling of response rate and a 17-week advantage in time to progression.
for adding lapatinib, an oral HER1-HER2 tyrosine kinase inhibitor, to capecitabine vs capecitabine alone among women with HER2-positive metastatic breast cancer that had recently progressed on chemotherapy/trastuzumab combination therapy (Figure 5).[14] This option may become commercially available in the near future. Another promising option to overcome trastuzumab resistance are the ansamycins, such as 17-allyl-amino-geldanamycin (17-AAG), which appear to cause degradation of the HER2 receptor, mediated in part by effects on the chaperone protein HSP-90.[47]

The ECOG has recently performed a trial comparing weekly paclitaxel[8,48] to weekly paclitaxel plus bevacizumab.[15] The addition of bevacizumab resulted in a doubling of response rate, and a 5 month prolongation of median time to progression (Figure 6). This agent will likely be the first antiangiogenic agent approved for breast cancer treatment, and has motivated similar study of other antiangiogenic agents, including sunitinib, an oral anti-VEGF and multikinase inhibitor. Sunitinib has demonstrated single-agent activity in anthracycline and taxane refractory disease,[35] among others.
Other agents on the horizon currently being studied in phase II and III clinical trials include those that inhibit various molecules involved in signaling pathways, such as farnesyl transferase, the mammalian target of rapamycin (mTOR), ras, raf-kinase, phosphoinositol-3-kinase, akt, MEK, and MAP-kinase, among others. As the intricate biology of breast cancer is further unraveled, and the development of novel targeted agents accelerates, it is likely that rational combinations of such agents will begin to replace cytotoxic chemotherapy in the management of advanced breast cancer.[49] Hopefully this will translate into significant prolongation of survival, in increments of years, rather than months, without significant added toxicity.

**Toward Better Selection of Available Therapy: Genomic and Proteomic Assays**

For the past 20 years, oncologists have largely been guided by the status of tumoral estrogen and progesterone receptors in selecting endocrine therapy, and only more recently, by HER2 status. The development of reliable assays to assess the true status of these biomarkers has been integral to the optimal application of agents targeting these proteins. Witness, for example, the uncertain benefit of trastuzumab in patients with tumors that overexpress HER2 as "2+" by immunohistochemistry, where the presence of HER2 gene amplification by fluorescence in situ hybridization better predicts therapeutic benefit.[49]

The ability of cytotoxic chemotherapy to increase the proportion of patients cured of early-stage breast cancer in indisputable. Also indisputable is the fact that many recipients of adjuvant...
chemotherapy will be cured without it, yet still experience toxicity from unnecessary chemotherapy. The ability to better select those patients, and in particular, those with lower-risk (eg, lymph node-negative breast cancer) who might be able to forego chemotherapy is of obvious value.

### Table 3

**TAILORx Study: Patient Selection and Primary Objectives**

**Patient Selection**
- ER- and/or PR-positive, lymph node–negative breast cancer
- HER2/neu negative (re: most HER2-positive have high RS)
- Meets standard guidelines for adjuvant chemotherapy
- Medically suitable candidates for chemotherapy
- Agreeable to have treatment assigned or randomized on the basis of the Oncotype DX test result

**Objectives**
- To determine whether adjuvant hormonal therapy (ie, experimental arm) is not inferior to adjuvant chemohormonal therapy (standard arm) for patients in the “primary study group” (Oncotype DX RS 11–25)
- To create a tissue and specimen bank for patients in this trial in order to evaluate new “clinical cancer tests”

ER = estrogen receptor; PR = progesterone receptor; RS = recurrence score.
Several recent studies have identified specific gene profiles in primary breast tumors that correlate with a greater likelihood of distant metastases.[16-19] One such assay, the Oncotype DX, has been validated as a prognostic test for patients with estrogen receptor-positive, node-negative breast cancer.[19] Patients with high recurrence scores have sufficiently high risk of recurrence to warrant the use of adjuvant chemotherapy, while those with low recurrence scores have sufficiently low risk as to be well-treated with antiestrogen therapy alone. A large prospective randomized phase III trial, PACCT-1, or TAILORx will determine whether patients with intermediate recurrence risk scores benefit from chemotherapy, or might perhaps be best treated with antiestrogen therapy alone (Tables 3 and 4, Figure 7).[20]
Conclusions
The past 20 years has witnessed an unparalleled expansion of knowledge of the molecular basis of breast cancer biology. In parallel, rationally designed targeted therapies have emerged, and are beginning to impact treatment of both advanced and early-stage disease.[50] The use of bisphosphonates to mitigate against skeletal complications of metastatic breast cancer has dramatically reduced the incidence of fractures, and with this, the need for radiotherapy and orthopedic surgery, as well as malignant hypercalcemia. A genomic-based assay of primary breast cancers has refined our ability to select those patients with estrogen receptor positive, node-negative breast cancer who might forego chemotherapy. It would appear from the amount of activity in new targeted agent development that we are indeed on the verge of the "beginning of the end of the chemotherapy era."

We have learned many lessons along the way. In the wake of reports of scientific misconduct,[44] honesty and accountability for data in clinical trials has made clinical investigators more meticulous and has led to increased quality control of clinical trials. We have learned that "size does matter"—the cooperation of cooperative oncology groups, the extension of clinical trials to community clinical oncology programs, and the development of global oncology networks (eg, BIG, BCIRG) has accelerated the pace at which very large, well-powered clinical trials can be completed. Such efforts require logistical support, technology, as well as a uniquely nonideologic and unselfish spirit of cooperation toward a common goal. Patient advocates have appropriately become part of the collective conscience of the oncology community, and have made important contributions in the direction of clinical research and in the choice of allocation of research funding.

We also now are faced increasingly with the dilemma of how health-care economies and individual patients will wrestle with higher costs of some new, effective, but expensive targeted therapies. Novel mechanisms of cooperation have evolved between government (the NIH/NCI/CTEP), the pharmaceutical/biotech industry, and academic centers to facilitate and streamline drug development (eg, Cooperative Research and Development Agreements [CRADA]). It is indeed a critical juncture, and one which affords much reason for optimism. Thoughtful integration of emerging targeted therapeutics, coupled with the ability to tailor systemic therapy to specific genomic subtypes of breast cancer promises to lead to larger incremental gains in progression-free and overall survival than we have become accustomed to seeing. During the next 2 decades, we will undoubtedly continue to witness progressive advances at a pace that will require frequent, clear and timely communication of such advances. This journal is proud to play no small part toward that purpose.

Disclosures:
Dr. Seidman is a member of the speakers' bureau and has received honoraria from Abraxis, Sanofi-Aventis, Bristol-Myers Squibb, Eli Lilly, Genentech, Amgen, Pfizer, Novartis, and Merck. He has
also served as a consultant for Pharmion, Sonus, and Cephalon.

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