Commentary

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Robert W. Carlson, MD

Robert W. Carlson, MD, joined NCCN as CEO in January 2013 after numerous leadership positions, including chair of the NCCN Breast Cancer Panel and several NCCN Task Forces. He has also been a member of the NCCN Breast Cancer Risk Reduction Panel, Breast Cancer Disease-Specific Executive Committee, CME Advisory Committee, Guidelines Steering Committee, and Board of Directors. Previously, and during the writing of this commentary, Dr. Carlson was Professor of Medicine in the Division of Oncology and Stanford Medical Informatics at Stanford University Medical Center. Dr. Carlson received his medical degree from Stanford University Medical School and completed his internship and junior residency in internal medicine at Barnes Hospital Group in St. Louis. He returned to Stanford for his senior residency and postdoctoral fellowship in medical oncology. Dr. Carlson is board certified in internal medicine and holds a subspecialty certification in medical oncology. Dr. Carlson is a member of several medical societies. He lectures extensively and has authored or co-authored over 130 articles, abstracts, and book chapters. He is also Associate Editor of *Oncology* and *JNCCN*.

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Ten Years of Progress Against Breast Cancer: A Partnership of Basic and Clinical/Translational Science

Robert W. Carlson, MD, on behalf of the NCCN Breast Cancer Panel

The past 10 years have witnessed multiple important advances in the systemic treatment of breast cancer (Table 1). These advances have resulted from a better understanding of the underlying biology of breast cancer, the development of new prognostic and predictive methods and new agents, and the better use of older agents. Moreover, these advances have led to a more selective application of agents targeted to refined subsets of breast cancer in both the adjuvant and metastatic settings.

Biology of Breast Cancer

Historically, systemic treatment decisions in early breast cancer were made primarily from an anatomic standpoint, and focused on risk of disease recurrence (prognostic factors) based on tumor size and grade; number of involved axillary lymph nodes; and, to a lesser extent, presence or absence of estrogen receptor (ER) and progesterone receptor (PR). In this paradigm, clinicians estimated the risk of recurrence and, if it was large enough, provided adjuvant chemotherapy and—if the tumor was ER+ and/or PR+—tamoxifen.

In the past decade, this approach was challenged by several findings. In 1998, a pivotal trial convincingly showed the clinical importance of tyrosine kinase signal transduction pathways by demonstrating that targeting the HER2 receptor with trastuzumab resulted in improved antitumor efficacy compared with chemotherapy alone in metastatic breast cancer overexpressing HER2.[1] This was rapidly followed by the initial reports of multigene array testing that showed that breast cancer could be grouped into important prognostic subtypes based on multigene expression profile.[2] The breast cancer subtypes identified by multigene array testing generally corresponded to the emerging biologic subtypes important to the selection of anti-tumor therapy: luminal A (ER+, HER2–), luminal B (ER+, HER2+/–), HER2+ (ER+/–, HER2+), or basal (ER–, PR–, HER2–).

This convergence of findings from the basic science laboratory with the clinically relevant and identified subtypes of breast cancer has been confirmed and has resulted in an inversion of the approach to disease stratification for systemic therapy. This was directly reflected in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer when the stratification of early breast cancer for systemic therapy was modified in 2006 into biologic subtypes based on ER, PR, and HER2 expression preceding stratification based on anatomic subsets (tumor size, grade, nodal status; to view the most recent version of the breast cancer guidelines, visit NCCN.org).

The recognition that breast cancer includes multiple biologically separate entities also refocused basic science, translational science, and clinical investigation of breast cancer into important biologic subtypes that could be approached with therapies targeting specific biologic vulnerabilities. This predicts that near-future advances in therapy are likely to emerge from refining the subtyping of breast cancer based on drug-targetable biochemical pathways differentially expressed by breast cancer subtypes and then specifically targeting those pathways for inhibition or facilitation.

Table 1 Milestones in the NCCN Clinical Practice Guidelines in Oncology for Breast Cancer

Year	Biology	Multigene Testing	Adjuvant Endocrine Therapy	HER2-Targeted Therapy	Adjuvant Chemotherapy	Chemotherapy for Metastatic Disease	Bone Health
2002			Anastrozole added as an option to tamoxifen in postmenopausal women				
2003						Listing of options divided into preferred single agents, preferred combination, and other active agents	Zoledronate added as an option to pamidronte in patients with bone metastasis
2004			Tamoxifen followed sequentially by an AI added as an option for postmenopausal women	Use of trastuzumab added in metastatic HER2+ disease	Option of dose-dense chemotherapy added as an option: doses and schedules of regimens specified		
2005			AI should be included for postmenopausal women	Use of trastuzimab in adjuvant therapy added			
2006	Stratification of women by ER/PR and HER2 subset for adjuvant therapy decisions	21-gene RT-PCR added as footnote				Option of bevacizumab added in combination with paclitaxel	
2007				Task Force recommendations on HER2 testing issued			
2008		21 gene RT-PCR test added for endrocrine-responsive, HER–, node-negative disease		Lapatinib added in combination with capecitabine	Option of docetaxel/ cyclophosphamide added	Option of ixabipalone added alone or in combination with capecitabine	
2009							
2010				Option of HER2-targeted therapy with AI therapy added			
2011						Option of eribulin added	Denosumab added as an option in patients with bone metastasis
2012	Retesting ER/ PR/HER2 in metastatic disease					Section on monitoring of metastic disease added	

Abbreviations: AI, aromatase inhibitor; ER, estrogen receptor; PR, progesterone receptor; RT-PCR, reverse-transcriptase polymerase chain reaction.

New Prognostic and Predictive Methods

The ability to stratify breast cancers into multigene expression subtypes has resulted in several investigations to develop multigene expression assay systems for prognostic and predictive purposes. In 2006, the NCCN Guidelines for Breast Cancer were the first major breast cancer guidelines to incorporate such a system, the 21-gene reverse-transcriptase polymerase chain reaction (RT-PCR) assay (Onco*type* DX). The NCCN Guidelines called for consideration of the use of the 21-gene RT-PCR assay to stratify patients with axillary lymph node–negative, hormone receptor–positive invasive breast cancer into 3 groups that predict magnitude of benefit from cytotoxic chemotherapy added to endocrine therapy in the adjuvant setting. Numerous other assay systems are available and have been validated to varying degrees, primarily for prognostic purposes. However, to date, the 21-gene RT-PCR assay is the only multigene assay incorporated into the NCCN Guidelines, primarily because of the ability to provide reliable estimates of overall prognosis and of expected benefit from the addition of cytotoxic chemotherapy.

The focus on the importance of determining the presence of ER, PR, and HER2 in stratifying patients for targeted therapy led to concerns about the reliability of biomarker testing in breast cancer. ASCO, the College of American Pathology, and NCCN issued technology assessments on methods to assure high-quality performance and interpretation of ER, PR, and HER2 testing.[3–6]

Evolution of Endocrine Therapy

Arguably, the most well-established finding in the treatment of breast cancer is that tamoxifen for 5 years in the adjuvant treatment of women with stage I to III hormone receptor–positive breast cancer improves disease-free and overall survival.[7] The effectiveness of aromatase inhibitors in the treatment of metastatic breast cancer led to a number of trials incorporating them into the adjuvant therapy of postmenopausal women with early-stage hormone receptor–positive breast cancer.[8] Most of the trials were restricted to women with ER+ breast cancer and compared tamoxifen with an aromatase inhibitor for 5 years, tamoxifen for 2 or 3 years followed by an aromatase inhibitor to complete 5 years of treatment, or 5 years of tamoxifen followed by an additional 5 years of an aromatase inhibitor.

These trials consistently showed superior disease-free and sometimes overall survival with the incorporation of an aromatase inhibitor. Reflecting the results of these trials, the NCCN Guidelines for Breast Cancer evolved over the past decade, adding anastrozole for 5 years as an option to tamoxifen in 2002, adding extended therapy with letrozole as an option after 5 years of tamoxifen in 2004, and stating that an aromatase inhibitor should be included in the treatment of postmenopausal women with hormone receptor–positive breast cancer, whether alone, sequentially with tamoxifen, or as extended adjuvant therapy, in 2005.[9] Recent data suggest that some patients with hormone receptor–positive, endocrine-resistant metastatic breast cancer may benefit from the addition of the mTOR inhibitor everolimus to exemestane.[10] The NCCN Guidelines for Breast Cancer were modified in 2012 to add everolimus plus exemestane as an option in the second-line endocrine treatment of postmenopausal women with hormone receptor–positive metastatic breast cancer.

Evolution of Cytotoxic Therapy

Cytotoxic chemotherapy improves outcomes in both the adjuvant and metastatic settings for many women with invasive breast cancer. Mathematical modeling predicted that the use of full-dose chemotherapy in short intervals ("dose-dense" therapy) would improve outcomes in the adjuvant treatment of breast cancer. Comparison of dose-dense versus non–dose-dense therapy did show improvement in disease-free and overall survivals in high-risk breast cancer.[11] The nonanthracycline regimen of docetaxel/cyclophosphamide showed superior time to relapse and overall survival versus doxorubicin/cyclophosphamide.[12] Both dose-dense therapy and docetaxel/cyclophosphamide were added to the list of appropriate adjuvant chemotherapy regimens.

The past decade has also witnessed the development of several new, active cytotoxic agents in the treatment of metastatic breast cancer. These include *nab*-paclitaxel, eribulin, and ixabepilone.

Evolution of HER2-Targeted Therapy

The use of trastuzumab, a humanized monoclonal antibody targeting the extracellular domain of HER2, in combination with chemotherapy in the treatment of HER2-overexpressing metastatic breast cancer was shown to improve time to progression and overall survival. This resulted in FDA approval in 1998,[1] and the use of trastuzumab in the metastatic setting was added to the NCCN Guidelines that same year. Clinical trials have documented improved outcomes with the addition of trastuzumab to several cytotoxic agents in metastatic HER2+ breast cancer.

In 2005, several randomized clinical trials of adjuvant cytotoxic chemotherapy with versus without trastuzumab

consistently demonstrated large and highly statistically significant reductions in recurrence rates and deaths.[13–16] These results literally altered the treatment of HER2+ breast cancer in the United States overnight, and trastuzumab-containing adjuvant chemotherapy regimens were added to the NCCN Guidelines in 2005.

Concerns regarding the accuracy of HER2 testing led to recommendations from both NCCN and ASCO/College of American Pathology regarding appropriate performance and interpretation of HER2 testing by both immunohistochemistry and fluorescence in situ hybridization.[3,4] Subsequent studies of lapatinib, a small molecule tyrosine kinase inhibitor targeting the intracellular domain of HER2, showed significant activity in combination with capecitabine in patients previously treated with trastuzumab.[17] In 2008, HER2 targeting with lapatinib alone versus with lapatinib and trastuzumab was studied in patients with metastatic breast cancer previously treated with trastuzumab. The study showed lapatinib plus trastuzumab was superior to lapatinib alone.[18]

Recently, the combination of pertuzumab, a monoclonal antibody that inhibits HER2 dimerization, with trastuzumab and docetaxel was shown to be superior to trastuzumab and docetaxel in the treatment of metastatic HER2+ breast cancer. The NCCN Guidelines were modified to incorporate combination pertuzumab, trastuzumab, and taxane as a preferred first-line regimen in HER2+ metastatic breast cancer.[19]

Confirming the impact of HER2-targeted therapies, combination endocrine therapy with an aromatase inhibitor alone or with either lapatinib or trastuzumab was also recently reported to prolong time to progression without impacting overall survival.[20,21]

Anti–Vascular Endothelial Growth Factor Therapy

Perhaps no other area of breast oncology has been as controversial over the past decade as the potential role of bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, in combination with chemotherapy for metastatic disease. An early trial of paclitaxel with or without bevacizumab in the first-line treatment of women with metastatic breast cancer showed that combination therapy increased rates of response and time to progression without significant prolongation in overall survival.[22] Based on the results of this initial study, the FDA provided accelerated approval of bevacizumab in combination with paclitaxel for first-line therapy of metastatic breast cancer. The use of bevacizumab plus paclitaxel was also added to the NCCN Guidelines as an option for metastatic breast cancer in 2006.

A number of other studies testing the role of bevacizumab in combination with docetaxel, capecitabine, and the anthracyclines have subsequently been reported,[23] showing no improvement in overall survival or in quality of life. The additional studies generally confirm increased rates of response and time to disease progression with the incorporation of bevacizumab. However, the magnitude of prolongation of overall time to progression seems more modest than in the initial paclitaxel study. Based on these additional studies, the FDA withdrew the indication for bevacizumab in the treatment of metastatic breast cancer in 2011. However, the NCCN Guidelines continue to include bevacizumab plus paclitaxel as a treatment option for patients with metastatic breast cancer.

Supportive Therapy

Women with bone metastases from breast cancer experience a high frequency of bone fracture, pain, and need for radiation therapy to boney sites. Early studies of pamidronate to prevent skeletal-related events confirmed its value in decreasing those events without direct impact on breast cancer or overall survival.[24] Subsequently, zoledronic acid and the monoclonal antibody denosumab have also been shown to reduce the frequency of skeletal-related events.[25,26] However, none of the bone-directed agents show a direct effect on breast cancer or overall survival in the metastatic setting. The agents are associated with an increase in frequency of electrolyte abnormalities and osteonecrosis of the jaw; bisphosphonates are also associated with renal insufficiency.

Conclusions

The NCCN Guidelines for Breast Cancer represent a dynamic, evolving series of treatment recommendations and options based on available scientific data and, when necessary, judgment and experience of expert panel members. Our improving understanding of the biology of breast cancer has allowed for the identification of subtypes that are most likely to benefit from specific, often targeted, agents. As the complexity of genetic subtyping, the understanding of signal transduction pathways, and the number of targetable biochemical pathways increase, the NCCN Guidelines will continue to evolve, reflecting the available scientific evidence that emerges from basic science and translational and clinical trials. Only through continued emphasis and participation in high-quality scientific studies and trials will further advances be achieved.

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