Cancer Control

Guest Editorial

Breast Cancer Treatment: Prospects for the Future

The past year has been exciting in terms of new developments for the treatment of breast cancer. Advances have been made in several different stages of disease. Women with metastatic breast cancer currently have several options for treatment that are generally well tolerated. Approval by the Food and Drug Administration (FDA) of trastuzumab (Herceptin) for the treatment of some patients with metastatic breast cancer has created much hope, but also an increasing amount of controversy. The new monoclonal growth factor antibody is a novel treatment for breast cancer and provides the first steppingstone in the development of biologic interventions for the treatment of the disease. Multitargeted therapy is the wave of the future for cancer treatment. Now more than ever, we need to foster research on mechanisms of cancer development and progression so that we can better understand how to develop agents specifically targeted against known cancer progression pathways.

The introduction of trastuzumab allows us to better appreciate this concept. The mechanism of action of trastuzumab is unclear, and the mechanisms of resistance are even more vague. Clinically, these mechanisms of resistance are important based on the low response rates observed in single-agent trials of trastuzumab in metastatic breast cancers that demonstrate HER-2 overexpression. The National Cancer Institute is sponsoring support for grant proposals investigating the mechanisms of action of trastuzumab. These investigations should allow us to better determine which subsets of breast cancer, besides those that overexpress HER-2, are likely to respond to trastuzumab. Metastatic breast cancers with HER-2 overexpression tend to have a lower response rate to chemotherapy when compared to historic chemotherapy treatment trial results. Thus, the most exciting outcome from the metastatic disease trials was the improved therapeutic index of chemotherapy combined with trastuzumab.

In this issue, Dr Edith Perez points out the importance of the variance in HER-2 testing of breast cancers. Initial reports generally used a monoclonal antibody that demonstrated a 25% to 30% incidence of HER-2 overexpression among all invasive breast cancers. More recently, a commercially available test uses a polyclonal antibody that may increase the sensitivity but decrease the specificity of HER-2 testing. This FDA-approved test is meant to be used not as a predictive test for determining specific breast cancer treatments, but rather as a therapeutic tool to determine candidacy for trastuzumab treatment.

Drs Massimo Cristofanilli and Gabriel Hortobagyi review the role of bisphosphonates, which comprise another exciting and controversial treatment for breast cancer. Bisphosphonates are well tolerated, and initial studies have shown an improvement in quality of life for patients with metastatic breast cancer affecting bones. Future research will focus on the mechanisms of action of these agents and the development of molecular markers to monitor response to therapy on these agents. The intriguing question of whether bisphosphonates can cure breast cancer by inhibiting micrometastasis in the adjuvant setting is raised by a small adjuvant trial suggesting that clodronate might improve survival above and beyond standard adjuvant therapy. The more potent third-generation agents are likely candidates to test this hypothesis. Many questions regarding bisphosphonates remain unanswered. Can bisphosphonates enhance the beneficial effects of chemotherapy and hormonal therapy? Do they have antitumor killing capabilities? Will they be more efficacious in the adjuvant setting than in the metastatic setting? Zolendronate is currently under investigation to compare its efficacy to pamidronate as an adjunct to usual therapy in the treatment of metastatic breast cancer, and adjuvant trials are being developed to investigate the impact of the addition of bisphosphonates to standard adjuvant therapy.

Research in new hormonal treatments for breast cancer is focusing on more potent ways to inhibit the estrogen receptor-mediated cancer progression pathways. New classes of agents are being developed to inhibit both the alpha and beta types of estrogen receptors as well as the ligands that interact with those receptors. The more potent selective inhibitors to the estrogen receptor are likely to have a higher response rate than standard hormonal agents that have partial estrogen-agonistic effects. The ultimate challenge is to develop a "designer" estrogen that not only reduces the risk of both breast cancer and uterine cancer, but also prevents menopausal side effects while maintaining beneficial effects on serum lipids and bone mineral density. Many of the new estrogen modulators are being developed for broad spectrum use in the setting of breast cancer prevention. The studies are focusing on postmenopausal women because the risk of breast cancer is higher with increasing age and because the prevention effects demonstrated to date seem to be limited to the estrogen receptor-positive breast cancers that are more commonly encountered in the postmenopausal population.

With increased awareness and education in screening and early detection of breast cancer, most women in the United States are diagnosed with early-stage disease. More women are having normal life expectancies after the adjuvant treatment of breast cancer and are currently faced with issues heretofore neglected. Fatigue seems to be an important component of toxicity from adjuvant chemotherapy and may be a substantial cause of long-term morbidity following therapy. Drs Paul Jacobsen and Kevin Stein present an interesting perspective on the problem of long-term fatigue after treatment of breast cancer. Why women experience such fatigue months to years following chemotherapy treatment remains to be determined. If some of the causes of fatigue could be identified, then developments in prevention could be initiated. Several questions regarding fatigue remain unanswered. Is significant fatigue a long-term complication in women with chemotherapy-induced premature menopause? Does chemotherapy induce other endocrine changes such as hypothyroid disease? Are there other mechanisms of fatigue that we are unaware of? Future research will address such issues and help to clarify this poorly understood topic.

Ductal carcinoma *in situ* (DCIS) of the breast is becoming an increasingly important part of breast cancer care. Dr Elisabeth Dupont and associates review the controversies concerning grading and staging this disease, and they provide the evidence that directs our modern management guidelines. They also describe the type of DCIS that is most likely to be associated with lymph node metastasis if the sentinel node technique and cytokeratin staining is used. Finally, they present the data that show that tamoxifen may have a role for some patients with this highly curable disease.

Young women diagnosed with breast cancer have yet another challenging issue to consider following treatment of early-stage disease. The safety of a subsequent pregnancy after a diagnosis of breast cancer is a frequent concern of women of childbearing age. Physicians have routinely asked women to wait two years following a diagnosis of breast cancer before becoming pregnant. This recommendation has not been based on any data showing that a particular length of time between a diagnosis of breast cancer and a subsequent pregnancy interferes with or worsens prognosis. The fear is that the elevated estrogen levels in pregnancy are detrimental in terms of increasing the risk of stimulating dormant micrometastatic cells. In this issue of *Cancer Control*, Drs Mary Gemignani and Jeanne Petrek provide a comprehensive review of the data on pregnancy subsequent to treatment for breast cancer. To date, no significant findings indicate that it is unsafe for women to undergo a pregnancy after a diagnosis of breast cancer. It is unlikely that prospective, randomized studies on this issue will be conducted. Therefore, it is important to consider contributing to the ongoing national database so that the number of breast cancer patients will be sufficient to further evaluate subsets for pregnancy-associated risk.

It is an exciting time to be involved in the treatment of breast cancer. Novel approaches to treatment are being developed to enhance standard therapy responses and to interfere with resistance mechanisms. Better understanding and further improvements in the long-term toxicities of treatment will significantly affect quality of life since most women diagnosed at an early stage of cancer now enjoy a normal life span. It is hoped that cancer therapy in the new millenium will be more targeted, less toxic, and ultimately more efficacious.

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