

Improving Breast Cancer Care

What an exciting era for breast cancer! Over the past two decades, data from studies involving widely disparate areas or research — ranging from the recognition of genetic patterns to targeted therapies — have been introduced into the management of breast cancer. This issue of *Cancer Control* reviews in detail a limited selection of these advances.

The opening paper by Dr. Robson discusses the clinical considerations pertinent to the management of hereditary breast and ovarian cancer. The review provides insight into the probability of an individual carrying a genetic mutation and describes the lifetime cancer risks associated with a BRCA1 or BRCA2 mutation. Surveillance and the clinical management of suggested and known genetic mutations are discussed, and concerns and ramifications of genetic testing are also presented. Two recent studies^{1,2} have confirmed what has been long assumed: Women with genetic mutations suggestive of a breast-ovarian syndrome may benefit from prophylactic salpingo-oophorectomy in terms of reducing the risk of developing ovarian cancer. What is more surprising is that these studies also found a reduction in breast cancer. This occurred despite the fact that the majority of women with BRCA1 mutations are likely to have estrogen receptor-negative breast cancers. Dr. Robson also addresses other available cancer risk-reduction strategies and highlights the

need for a multidisciplinary approach to women with familial or hereditary breast cancer.

In the second paper, Dr. Minton and I discuss chemotherapy-induced amenorrhea and fertility issues pertinent to young women with breast cancer. The preservation of fertility has become a more important issue as the number of older women who want to have children increases and as more young women are diagnosed with breast cancer. A plethora of studies have suggested that with the exception of very small tumors, young women with early-stage breast cancer receive and benefit from adjuvant cytotoxic chemotherapy. As more women survive breast cancer, the long-term sequelae of treatment become more relevant. In most cases, chemotherapy imposes a significant risk to ovarian function, particularly in women who are in their late 30s and early 40s. We review the literature in terms of the course of natural menopause and fertility and the potential effects of chemotherapy on these parameters with regard to age and type of regimen. The preservation of ovarian function and fertility are questions currently being studied by the authors in a phase II randomized trial that evaluates the use of LHRH agonists during adjuvant chemotherapy.

Dr. Newman and Dr. Blake then discuss the use of the relatively new modality of ductal lavage in

risk assessment for breast cancer. Prevention of breast cancer has become the focus of intense research. The currently available modalities include surgical or chemical hormonal manipulation or prophylactic mastectomy. While the former may not be sufficiently effective, the latter is a drastic step and, albeit effective, is associated with appreciable emotional and physical distress. Therefore, definitions of “high-risk” that would pertain to individuals rather than to populations would be of great help for those women who are considering breast cancer preventive measures. The optimal timing of preventive interventions is still uncertain. The authors present currently available information on ductal lavage and summarize its potential benefits as a risk assessment tool as well as for other uses.

Next, Dr. Van Poznak reviews the benefits of bisphosphonates in breast cancer. Several bisphosphonates are currently available in oral or intravenous forms. Bisphosphonates have a well-established role not only in treating hypercalcemia and bone pain, but also in reducing the risk of fractures in patients with bone metastasis. Whether bisphosphonates reduce the risk of developing bone metastasis is controversial and is being currently addressed in two large randomized trials (NSABP B-34 and SWOG 9905). Dr. Van Poznak also delineates the safety and potential renal complications of these drugs. The

long-term safety of bisphosphonates and optimal target populations will become even more pertinent issues since the aromatase inhibitors, which have been shown to enhance bone loss, have already entered the adjuvant setting.

The role of aromatase inhibitors in the prevention and treatment of breast cancer is discussed by Dr. Lake and Dr. Hudis in the following paper. Over the last few years, several studies have determined that the aromatase inhibitors are effective and tolerable alternatives to tamoxifen in the treatment of hormone-sensitive advanced breast cancer, and the Food and Drug Administration recently approved the use of anastrozole for the adjuvant treatment of early-stage breast cancer. This approval was based on the report of a study involving more than 9,300 women with hormone-sensitive, early-stage breast cancers in more than 20 countries. Despite a relatively short-term follow-up of 33 months, the study suggested that the use of anastrozole is at least as effective if not superior to tamoxifen in terms of disease-free survival and the prevention of contralateral breast cancer. At least for the duration of the study, anastrozole appeared safe and tolerable with fewer untoward effects on the uterus and fewer serious thromboembolic events than tamoxifen. However, anastrozole was associated with negative effects on bone mineralization. While these findings are exciting and have introduced an alternative to tamoxifen, the report has fostered many questions: What are the long-term

effects of aromatase inhibitors, particularly on bone health and cognition? What about the patients currently on tamoxifen, or after 5 years of tamoxifen treatment? Which of the three currently approved aromatase inhibitors should be prescribed? This article updates the reader on the currently ongoing research in the quest to answer some of these questions.

In the last article, Dr. Horton reports the advances in the use of trastuzumab. The introduction of the monoclonal humanized antibody against HER2 has given hope to a group of patients with tumors that are associated with shorter relapse-free and overall survival. After the proof of principle in HER2 targeting was established and most of the hurdles in determining the optimal tests to quantify HER2 expression were overcome, the current questions evolving around the use of trastuzumab are of a more of practical nature: Should trastuzumab be used alone or in combination with cytotoxic agents? Which cytotoxic agent? Should trastuzumab be continued upon progression? How is cardiotoxicity managed and explained? Is trastuzumab safe enough for adjuvant use? This article summarizes the current data that address some of these issues. And then, of course, there is the mystery of the opposing vs complementing effects of immune-mediated cytotoxicity vs inhibition of cell-signaling pathways, and what determines herceptin resistance! These last questions will be of importance in the further development of anti-HER2 therapies.

The present is an exciting time for researchers and clinicians who care for patients with breast cancer. However, there is still much to learn about the molecular makeup of this disease and how to more effectively and selectively prevent and treat a disease that will affect more than one in every 10 women. Advances are reported daily, so the oncologist has the critical job of sifting through the mountains of material on new approaches in order to apply not just the latest enhancements, but also the well-validated and effective improvements to patient care that will maximize the benefit to those with breast cancer or at risk for developing the disease.

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